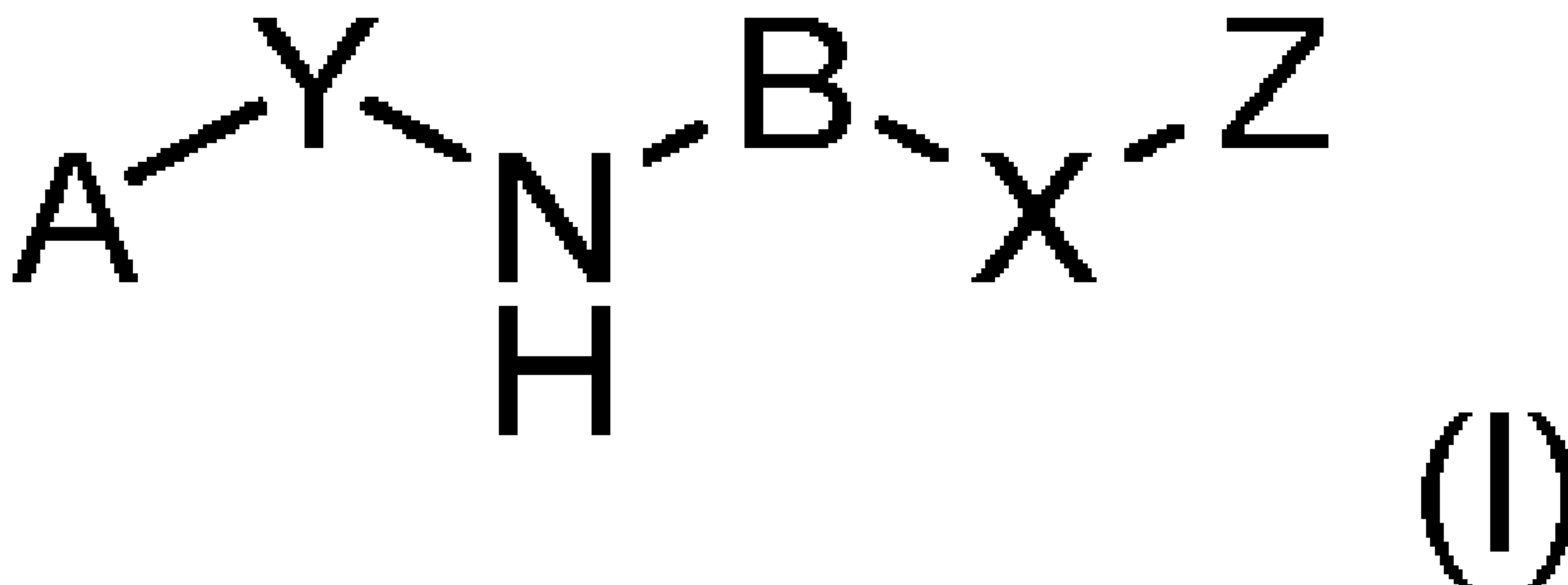




(86) **Date de dépôt PCT/PCT Filing Date:** 2015/09/09
(87) **Date publication PCT/PCT Publication Date:** 2016/03/17
(85) **Entrée phase nationale/National Entry:** 2017/03/03
(86) **N° demande PCT/PCT Application No.:** US 2015/049221
(87) **N° publication PCT/PCT Publication No.:** 2016/040505
(30) **Priorités/Priorities:** 2014/09/10 (US62/048,773);
2015/04/13 (US62/146,799)

(51) **Cl.Int./Int.Cl. A01N 43/54** (2006.01),
A61K 31/517 (2006.01)
(71) **Demandeur/Applicant:**
EPIZYME, INC., US
(72) **Inventeurs/Inventors:**
FOLEY, MEGAN ALENE CLOONAN, US;
KUNTZ, KEVIN WAYNE, US;
MILLS, JAMES EDWARD JOHN, GB;
MITCHELL, LORNA HELEN, US;
MUNCHHOF, MICHAEL JOHN, US;
HARVEY, DARREN MARTIN, US
(74) **Agent:** BORDEN LADNER GERVAIS LLP

(54) **Titre : INHIBITEURS DE SMYD**
(54) **Title: SMYD INHIBITORS**



(57) **Abrégé/Abstract:**

The present disclosure provides carboxamides and sulfonamides having Formula (I): and the pharmaceutically acceptable salts and solvates thereof, wherein A, Y, B, X, and Z are defined as set forth in the specification. The present disclosure is also directed to the use of compounds of Formula (I) to treat a disorder responsive to the blockade of SMYD proteins such as SMYD3 or SMYD2. Compounds of the present disclosure are especially useful for treating cancer.



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



WIPO | PCT



(10) International Publication Number

WO 2016/040505 A1

(43) International Publication Date
17 March 2016 (17.03.2016)

(51) International Patent Classification:

A01N 43/54 (2006.01) A61K 31/517 (2006.01)

(21) International Application Number:

PCT/US2015/049221

(22) International Filing Date:

9 September 2015 (09.09.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/048,773 10 September 2014 (10.09.2014) US
62/146,799 13 April 2015 (13.04.2015) US

(71) Applicant: EPIZYME, INC. [US/US]; 400 Technology Square, 4th Floor, Cambridge, Massachusetts 02139 (US).

(72) Inventors: FOLEY, Megan Alene Cloonan; 34 Alpine St., Somerville, Massachusetts 02144 (US). KUNTZ, Kevin Wayne; 8 New Village Rd, Woburn, Massachusetts 01801 (US). MILLS, James Edward John; Holly End, The Street, Worth, Deal Kent CT14 0DF (GB). MITCHELL, Lorna Helen; 1 Nichols Place, Cambridge, Massachusetts 02138 (US). MUNCHHOF, Michael John; 266 West Road, Salem, Connecticut 06420 (US). HARVEY, Darren Martin; 3 Barker Road, Acton, Massachusetts 01720 (US).

(74) Agents: COVERT, John M. et al.; Sterne, Kessler, Goldstein & Fox P.L.L.C, 1100 New York Avenue, N.W., Washington, District of Columbia 20005 (US).

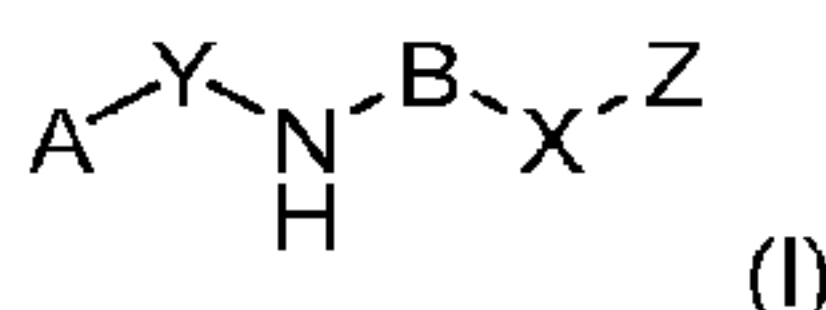
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- with sequence listing part of description (Rule 5.2(a))

(54) Title: SMYD INHIBITORS



(57) Abstract: The present disclosure provides carboxamides and sulfonamides having Formula (I): and the pharmaceutically acceptable salts and solvates thereof, wherein A, Y, B, X, and Z are defined as set forth in the specification. The present disclosure is also directed to the use of compounds of Formula (I) to treat a disorder responsive to the blockade of SMYD proteins such as SMYD3 or SMYD2. Compounds of the present disclosure are especially useful for treating cancer.



WO 2016/040505 A1

SMYD INHIBITORS

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present disclosure provides carboxamides and sulfonamides as SMYD protein inhibitors, such as SMYD3 and SMYD2 inhibitors, and therapeutic methods of treating conditions and diseases wherein inhibition of SMYD proteins such as SMYD3 and SMYD2 provides a benefit.

Background

[0002] Epigenetic regulation of gene expression is an important biological determinant of protein production and cellular differentiation and plays a significant pathogenic role in a number of human diseases. Epigenetic regulation involves heritable modification of genetic material without changing its nucleotide sequence. Typically, epigenetic regulation is mediated by selective and reversible modification (*e.g.*, methylation) of DNA and proteins (*e.g.*, histones) that control the conformational transition between transcriptionally active and inactive states of chromatin. These covalent modifications can be controlled by enzymes such as methyltransferases (*e.g.*, SMYD proteins such as SMYD3 and SMYD2), many of which are associated with genetic alterations that can cause human disease, such as proliferative disorders. Thus, there is a need for the development of small molecules that are capable of inhibiting the activity of SMYD proteins such as SMYD3 and SMYD2.

BRIEF SUMMARY OF THE INVENTION

[0003] In one aspect, the present disclosure provides carboxamido and sulfonamide compounds represented by Formulae **I-XVIII** below, and the pharmaceutically acceptable salts and solvates thereof, collectively referred to herein as "Compounds of the Disclosure."

[0004] In another aspect, the present disclosure provides a Compound of the Disclosure and one or more pharmaceutically acceptable carriers.

[0005] In another aspect, the present disclosure provides a method of inhibiting SMYD proteins, such as SMYD3 or SMYD2, or both, in a mammal, comprising

administering to the mammal an effective amount of at least one Compound of the Disclosure.

[0006] In another aspect, the present disclosure provides methods for treating a disease, disorder, or condition, *e.g.*, cancer, responsive to inhibition of SMYD proteins, such as SMYD3 or SMYD2, or both, comprising administering a therapeutically effective amount of a Compound of the Disclosure.

[0007] In another aspect, the present disclosure provides the use of Compounds of the Disclosure as inhibitors of SMYD3.

[0008] In another aspect, the present disclosure provides the use of Compounds of the Disclosure as inhibitors of SMYD2.

[0009] In another aspect, the present disclosure provides the use of Compounds of the Disclosure as inhibitors of SMYD proteins.

[0010] In another aspect, the present disclosure provides a pharmaceutical composition for treating a disease, disorder, or condition responsive to inhibition of SMYD proteins, such as SMYD3 or SMYD2, or both, wherein the pharmaceutical composition comprises a therapeutically effective amount of a Compound of the Disclosure in a mixture with one or more pharmaceutically acceptable carriers.

[0011] In another aspect, the present disclosure provides Compounds of the Disclosure for use in treating cancer in a mammal, *e.g.*, breast, cervical, colon, kidney, liver, head and neck, skin, pancreatic, ovary, esophageal, lung, and prostate cancer.

[0012] In another aspect, the present disclosure provides a Compound of the Disclosure for use in the manufacture of a medicament for treating cancer in a mammal.

[0013] In another aspect, the present disclosure provides kit comprising a Compound of the Disclosure.

[0014] Additional embodiments and advantages of the disclosure will be set forth, in part, in the description that follows, and will flow from the description, or can be learned by practice of the disclosure. The embodiments and advantages of the disclosure will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

[0015] It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only, and are not restrictive of the invention as claimed.

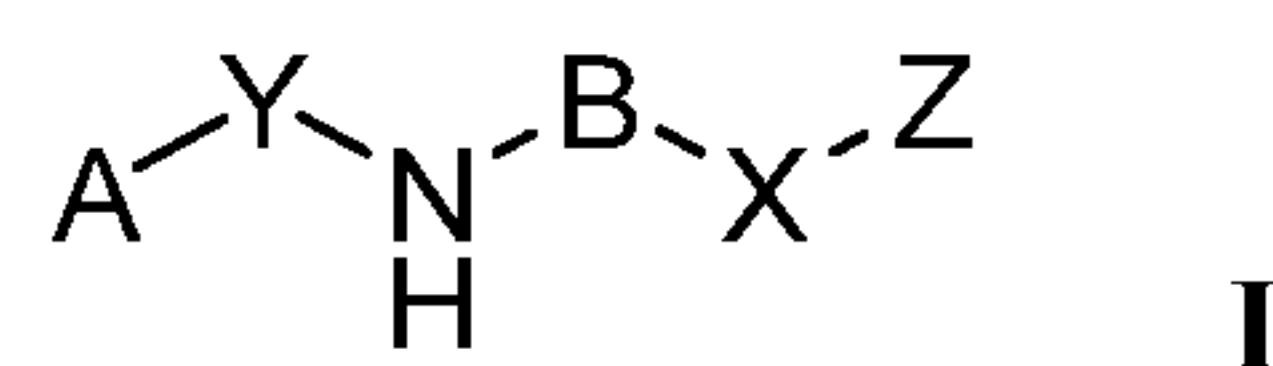
DETAILED DESCRIPTION OF THE INVENTION

[0016] One aspect of the present disclosure is based on the use of Compounds of the Disclosure as inhibitors of SMYD proteins. In view of this property, the Compounds of the Disclosure are useful for treating diseases, disorders, or conditions, *e.g.*, cancer, responsive to inhibition of SMYD proteins.

[0017] One aspect of the present disclosure is based on the use of Compounds of the Disclosure as inhibitors of SMYD3. In view of this property, the Compounds of the Disclosure are useful for treating diseases, disorders, or conditions, *e.g.*, cancer, responsive to inhibition of SMYD3.

[0018] One aspect of the present disclosure is based on the use of Compounds of the Disclosure as inhibitors of SMYD2. In view of this property, the Compounds of the Disclosure are useful for treating diseases, disorders, or conditions, *e.g.*, cancer, responsive to inhibition of SMYD2.

[0019] In one embodiment, Compounds of the Disclosure are compounds having Formula I:



and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein:

[0020] A is selected from the group consisting of 1,2,3-triazolyl, 1,2,4-triazolyl, 1-imidazolyl, 1-isoquinolyl, 1-pyrazolyl, 2-(1,2,3,4-tetrahydroquinolyl), 2-benzo[d]imidazolyl, 2-benzo[d]thiazolyl, 2-chromenyl-4-one, 2-furanyl, 2-imidazo[1,2-b]pyridazinyl, 2-imidazolyl, 2-indolyl, 2-naphthalenyl, 2-pyrazinyl, 2-pyridyl, 2-pyrimidinyl, 2-pyrrolidinyl, 2-pyrrolyl, 2-quinolyl, 2-quinoxalyl, 2-thiazolo[5,4-c]pyridinyl, 2-thiazolyl, 2-thiophenyl, 3-(1,2,3,4-tetrahydroisoquinoline), 3-(1,2,4-oxadiazolyl), 3-imidazo[1,2-a]pyrimidinyl, 3-indazolyl, 3-indolyl, 3-isothiazolyl, 3-pyrazolyl, 3-pyridazinyl, 3-pyridinyl-2-one, 3-pyridyl, 3-pyrrolo[3,2-b]pyridinyl, 3-quinolyl, 4-(2,2-difluorobenzo[d][1,3]dioxolyl), 4-cyclohexanyl-1-amine, 4-imidazolyl, 4-indolinyl-2-one, 4-indolyl, 4-isothiazolyl, 4-oxazolyl, 4-piperidinyl, 4-pyrazolyl, 4-pyridyl, 4-quinolyl, 5-(1,3-dihydro-2H-benzo[d]imidazolyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-b]pyridinyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-c]pyridinyl-2-one), 5-(2,2-difluorobenzo[d][1,3]dioxolyl), 5-(2,4-dihydro-3H-1,2,4-triazolyl-3-one), 5-4H-furo[3,2-b]pyrrolyl, 5-benzo[c][1,2,5]oxadiazolyl, 5-benzo[d][1,3]dioxolyl,

5-benzo[d]oxazolyl-2(3H)-one, 5-bicyclo[2.2.1]heptyl-2-ene, 5-indolinyl-2,3-dione, 5-indolinyl-2-one, 5-indolyl, 5-isoindolinyl-1-one, 5-isoxazolyl, 5-pyrazolo[3,4-c]pyridinyl, 5-pyrazolyl, 5-pyrimidinyl, 5-thiazolyl, 6-(1,2,3,4-tetrahydronaphthalenyl), 6-(3,4-dihydroquinolinyl-2(1H)-one), 6-(3,4-dihydroquinoxalinyl-2(1H)-one), 6-(4,5-dihydropyridazinyl-3(2H)-one), 6-benzo[b][1,4]oxazinyl-3-one, 6-benzo[d]imidazolyl, 6-benzo[d]oxazolyl-2(3H)-one, 6-benzo[d]thiazolyl, 6-chromenyl-2-one, 6-imidazo[2,1-b]thiazole, 6-indazolyl, 6-indolinyl-2-one, 6-indolyl, 6-isoquinolinyl, 6-quinolinyl, 6-quinoxalinyl, 6-quinoxalinyl-2(1H)-one, 7-(3,4-dihydroquinolinyl-2(1H)-one), 7-(3,4-dihydroquinoxalin-2(1H)-one), 7-benzo[b][1,4]oxazinyl-3-one, 7-indolinyl-2-one, 7-quinolinyl, 8-benzo[b][1,4]oxazinyl-3-one, cyclopropanyl, phenyl, 4-(prop-1-en-1-yl)-imidazole, 1-butanyl-imidazole, sec-butylcyclopropane, 2-(ethylsulfonyl)propanyl, 1-isobutylpyrrolidine, 4-pyridyl 1-oxide, and 5-benzo[c][1,2,5]oxadiazolyl 1-oxide,

[0021] each of which is optionally substituted with one, two, or three substituents independently selected from the group consisting of halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, C₁₋₆ alkyl, haloalkyl, hydroxyalkyl, (carboxamido)alkyl, (cycloalkyl)alkyl, optionally substituted C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 5- to 14-membered heteroaryl, optionally substituted 4- to 14-membered heterocyclo, aralkyl, -N(H)C(=O)R⁶, -C(=O)R⁷, and -S(=O)₂R⁸;

[0022] Y is selected from the group consisting of -C(R^{5a})(R^{5b})C(=O)-, -C(=O)-, and -S(=O)₂-;

[0023] B is selected from the group consisting of C₁₋₁₀ alkylenyl, optionally substituted C₃₋₁₂ cycloalkylenyl, optionally substituted C₆₋₁₄ arylenyl, optionally substituted 4- to 14-membered heterocyclenyl, and -C(H)R¹R²,

[0024] with the proviso that B is not optionally substituted pyrrolidinenyl;

[0025] X is selected from the group consisting of -N(R³)-, -S(=O)₂-, -S(=O)₂N(R³)-, -N(R³)S(=O)₂-, -S(=O)₂C(R⁴)(H)-, -C(=O)-, -C(=O)N(R³)-, -N(R³)C(=O)-, -C(=O)O-, -OC(=O)-, -C(=O)C(R⁴)(H)N(R³)-, -N(R³)C(=O)C(R⁴)(H)-, and -C(=O)C(R⁴)(H)-; or X is absent, i.e., Z forms a bond with B;

[0026] Z is selected from the group consisting of hydrogen, optionally substituted C₁₋₆ alkyl, fluoroalkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, (cycloalkyl)alkyl, (amino)(hydroxy)alkyl, (amino)(aryl)alkyl, (hydroxy)(aryl)alkyl, (aralkylamino)alkyl,

(hydroxyalkylamino)alkyl, alkoxyalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C₃₋₁₂ cycloalkyl, aralkyl, and (heteroaryl)alkyl; or

[0027] Z is -CH(R^{9a})(R^{9b});

[0028] R^{9a} is selected from the group consisting of hydrogen, C₁₋₆ alkyl, fluoroalkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, alkoxyalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C₃₋₁₂ cycloalkyl, aralkyl, and (heteroaryl)alkyl;

[0029] R^{9b} is selected from the group consisting of optionally substituted C₆₋₁₄ aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C₃₋₁₂ cycloalkyl, aralkyl, and (heteroaryl)alkyl;

[0030] R¹ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, optionally substituted C₃₋₁₂ cycloalkyl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted C₆₋₁₄ aryl, aralkyl, and alkoxycarbonyl;

[0031] R² is selected from the group consisting of C₁₋₆ alkyl, optionally substituted C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 5- to 14-membered heteroaryl, optionally substituted 4- to 14-membered heterocyclo, and (heteroaryl)alkyl;

[0032] R³ is selected from the group consisting of hydrogen and C₁₋₄ alkyl; and

[0033] R⁴ is selected from the group consisting of hydrogen, C₁₋₄ alkyl, hydroxy, amino, alkylamino, dialkylamino, cycloalkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, and hydroxyalkyl.

[0034] R^{5a} is selected from the group consisting of hydrogen and C₁₋₄ alkyl;

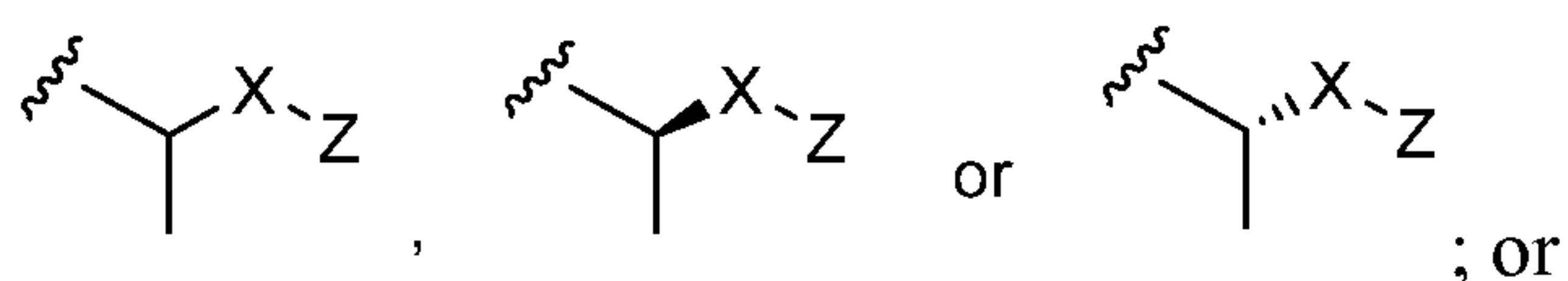
[0035] R^{5b} is selected from the group consisting of hydrogen, C₁₋₄ alkyl, and 4- to 14-membered heterocyclo;

[0036] R⁶ is C₁₋₄ alkyl,

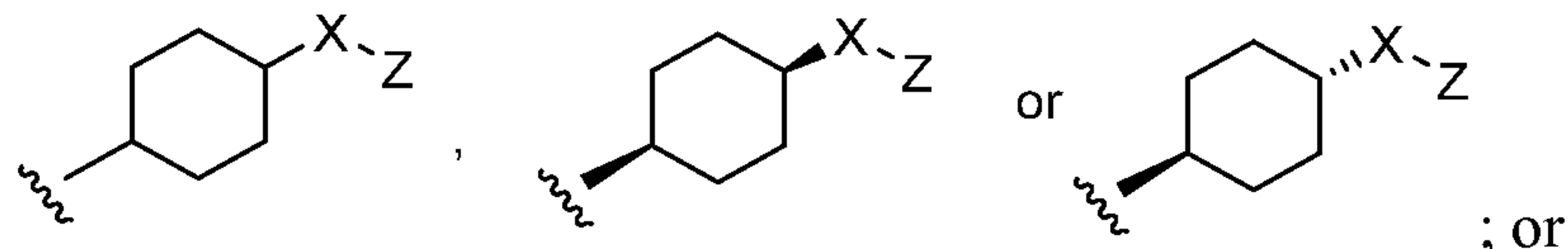
[0037] R⁷ is C₁₋₄ alkyl; and

[0038] R⁸ is selected from the group consisting of C₁₋₄ alkyl, amino, alkylamino, and dialkylamino,

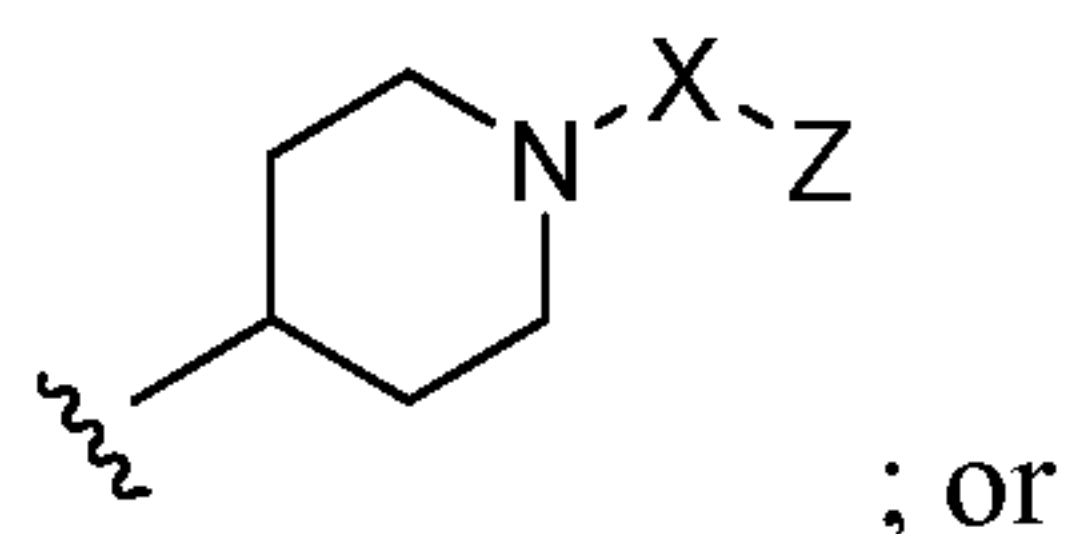
- [0039] wherein -X-Z is attached to any available carbon or nitrogen atom of B, R¹, or R², *e.g.*, when R² is C₁₋₆ alkyl, *e.g.*, ethyl, a hydrogen atom of that ethyl group is replaced with -X-Z to give -CH₂CH₂-X-Z or



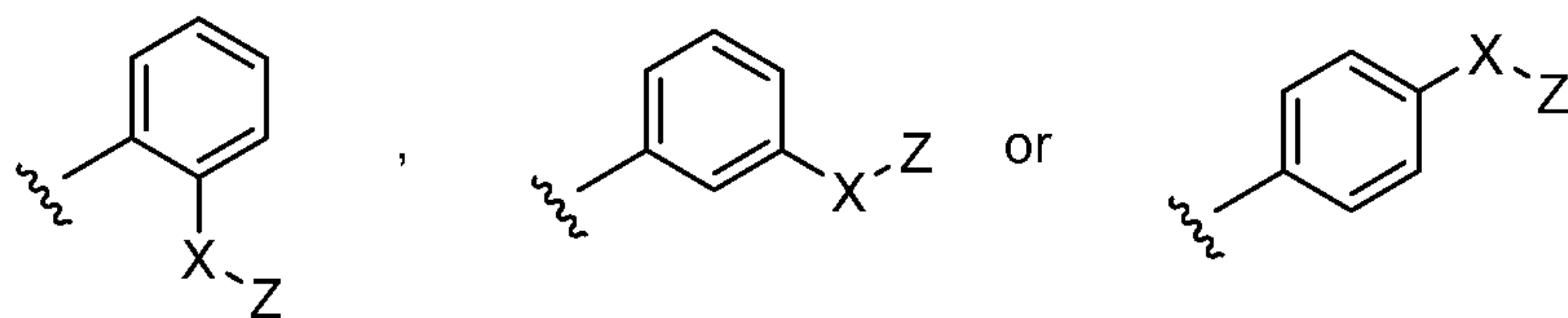
- [0040] when R² is optionally substituted C₃₋₁₂ cycloalkyl, *e.g.*, cyclohexyl, a hydrogen atom of the cyclohexyl group is replaced with -X-Z to give:



- [0041] when R² is optionally substituted 4- to 14-membered heterocyclo, *e.g.*, piperidiny, the hydrogen atom attached to the piperidiny nitrogen atom is replaced with -X-Z to give:



- [0042] when R² is optionally substituted C₆₋₁₄ aryl, *e.g.*, phenyl, a hydrogen atom on that phenyl group is replaced with -X-Z to give:



- [0043] In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Z is selected from the group consisting of hydrogen, optionally substituted C₁₋₆ alkyl, fluoroalkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, (cycloalkyl)alkyl, (amino)(hydroxy)alkyl, (amino)(aryl)alkyl, (hydroxy)(aryl)alkyl, (aralkylamino)alkyl, (hydroxyalkylamino)alkyl, alkoxyalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C₃₋₁₂ cycloalkyl, aralkyl, and (heteroaryl)alkyl.

- [0044] In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein X is absent.

In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein X is absent; B is optionally substituted 4- or 6- to 14-membered heterocyclenyl; and Z is selected from the group consisting of hydrogen, optionally substituted C₁₋₆ alkyl, fluoroalkyl, hydroxyalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C₃₋₁₂ cycloalkyl, aralkyl, and (heteroaryl)alkyl.

[0045] In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is optionally substituted 4- or 6- to 14-membered heterocyclenyl; X is absent; and Z is -CH(R^{9a})(R^{9b}).

[0046] In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is optionally substituted 4- or 6- to 14-membered heterocyclenyl; X is absent; and Z is -CH(R^{9a})(R^{9b}), wherein:

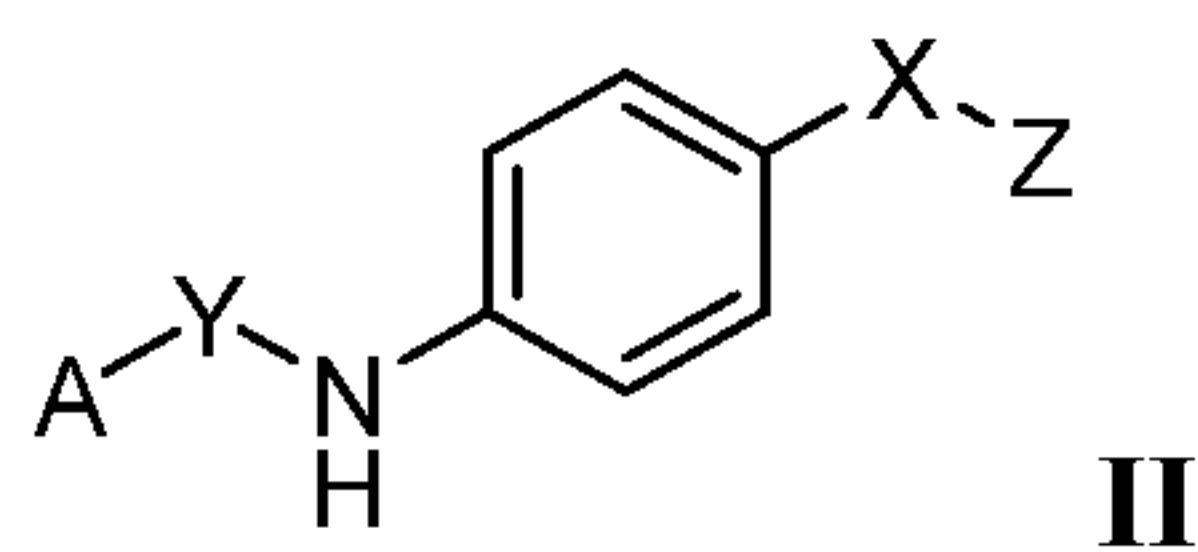
[0047] R^{9a} is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and optionally substituted C₃₋₁₂ cycloalkyl; and

[0048] R^{9b} is selected from the group consisting of optionally substituted C₆₋₁₄ aryl, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C₃₋₁₂ cycloalkyl, aralkyl, and (heteroaryl)alkyl.

[0049] In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is C₁₋₁₀ alkylenyl. In another embodiment, X is selected from the group consisting of -N(R³)C(=O)C(R⁴)(H)- and -N(R³)C(=O)-. In another embodiment, Z is selected from the group consisting of C₁₋₆ alkyl and (amino)alkyl.

[0050] In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is optionally substituted C₆₋₁₄ arylenyl. In another embodiment, B is divalent form of optionally substituted phenyl.

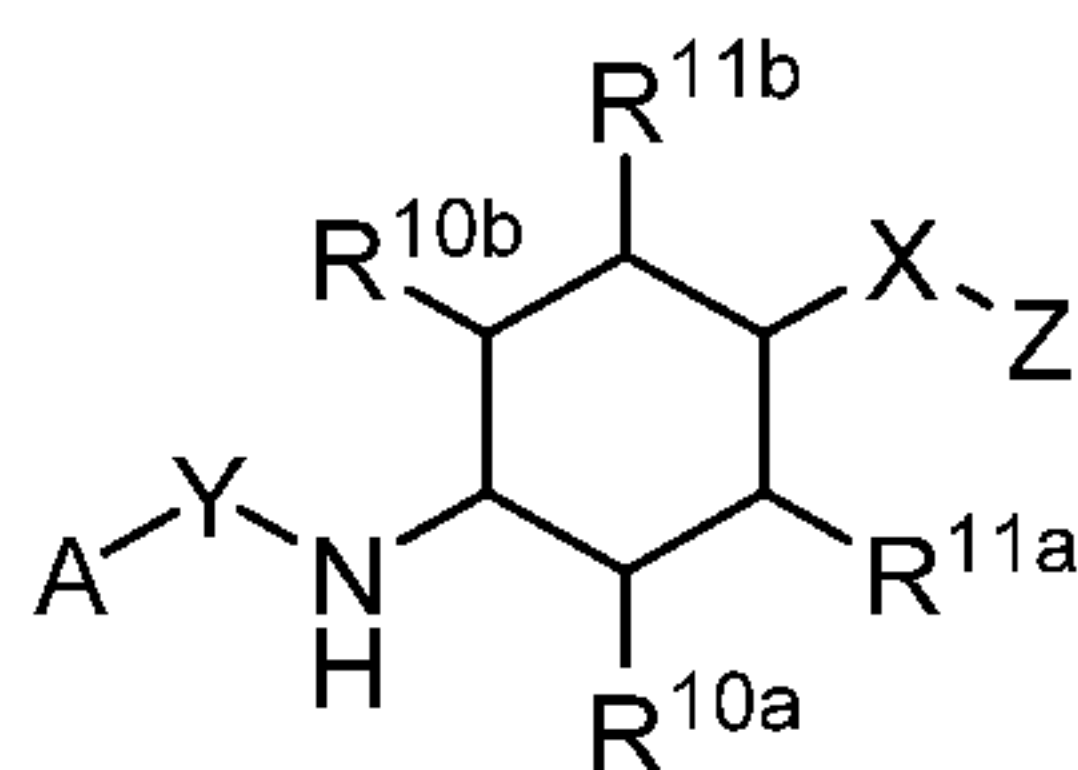
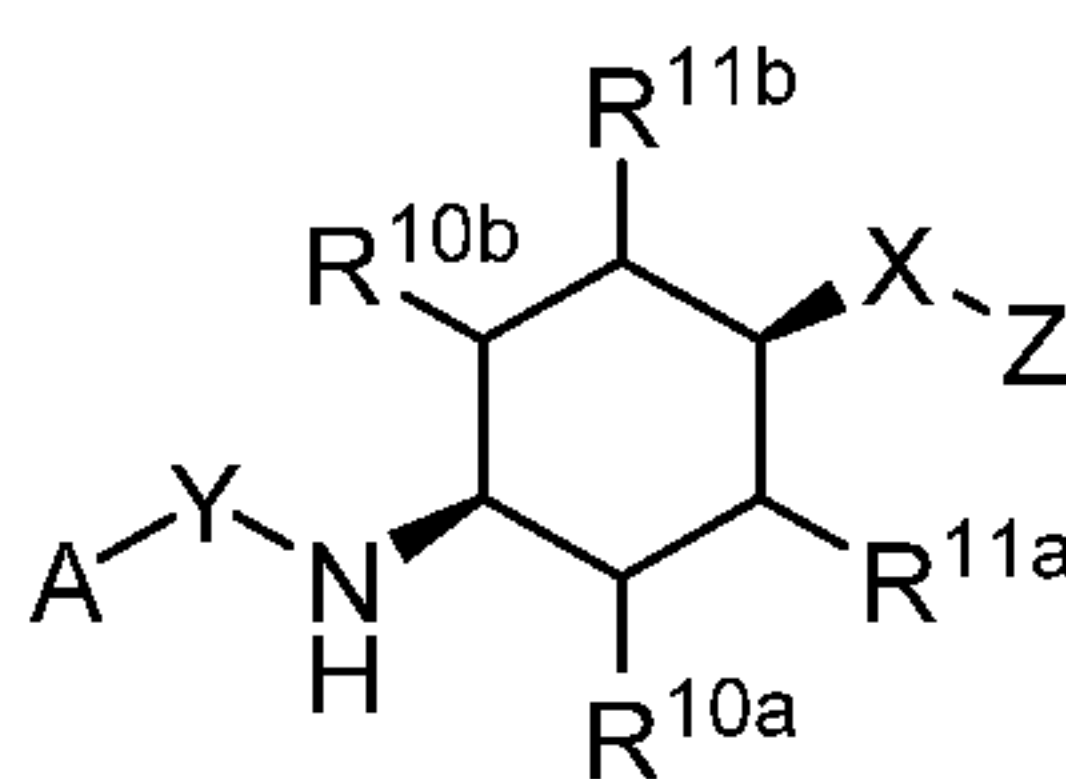
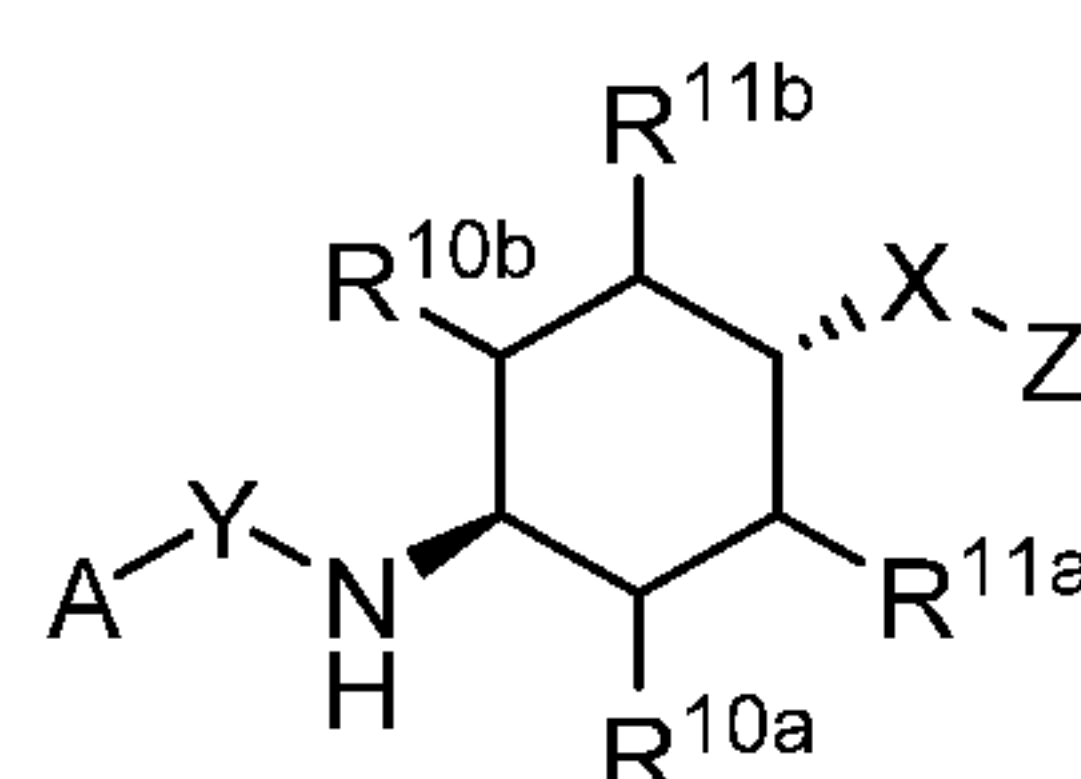
[0051] In another embodiment, Compounds of the Disclosure are compounds having Formula II:



and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein X is absent and Z is (amino)alkyl; and A and Y are as defined above in connection with Formula I.

[0052] In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is optionally substituted C₃₋₁₂ cycloalkylenyl.

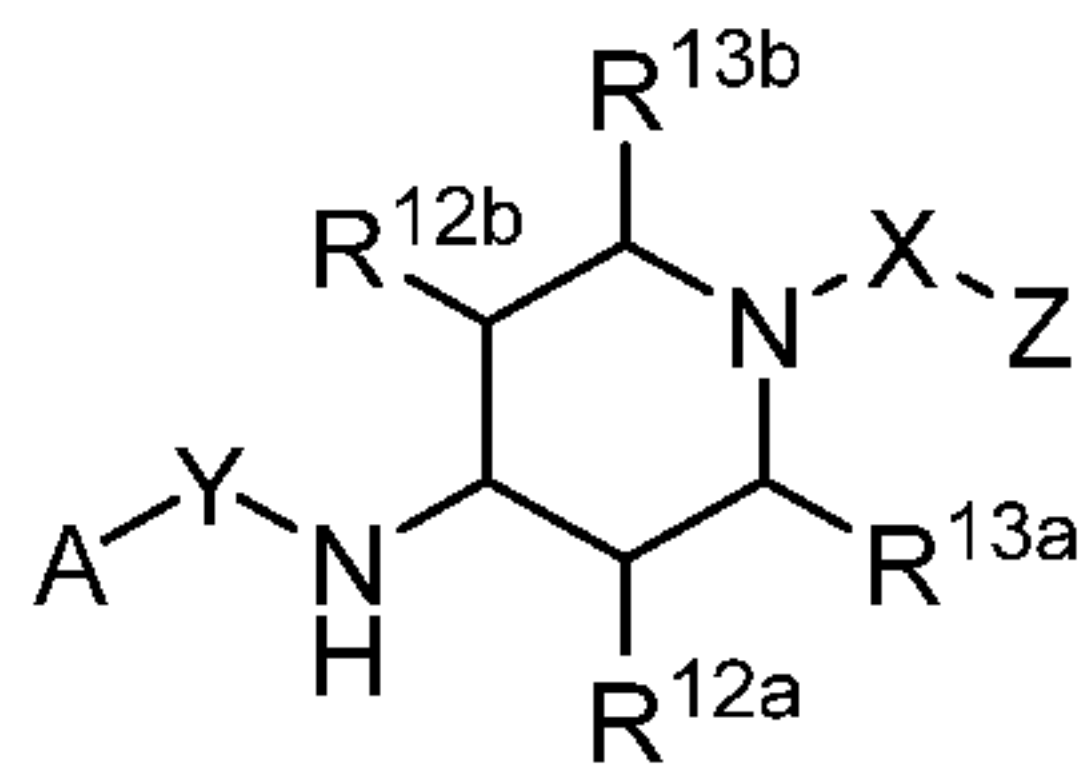
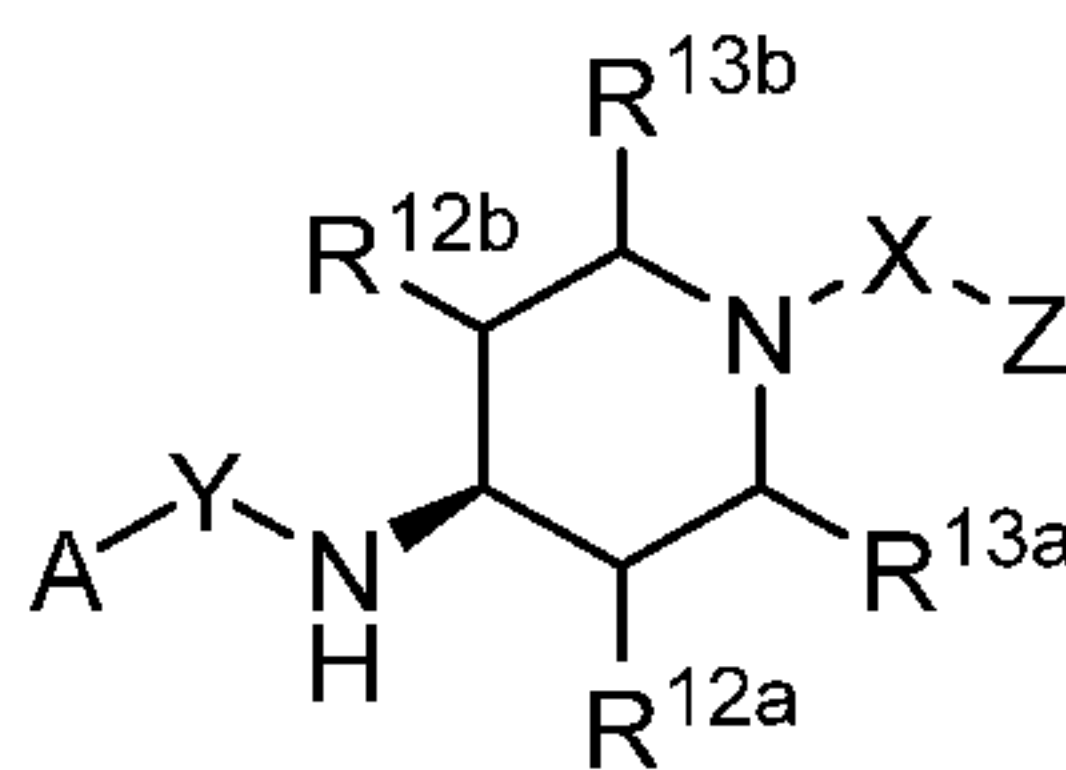
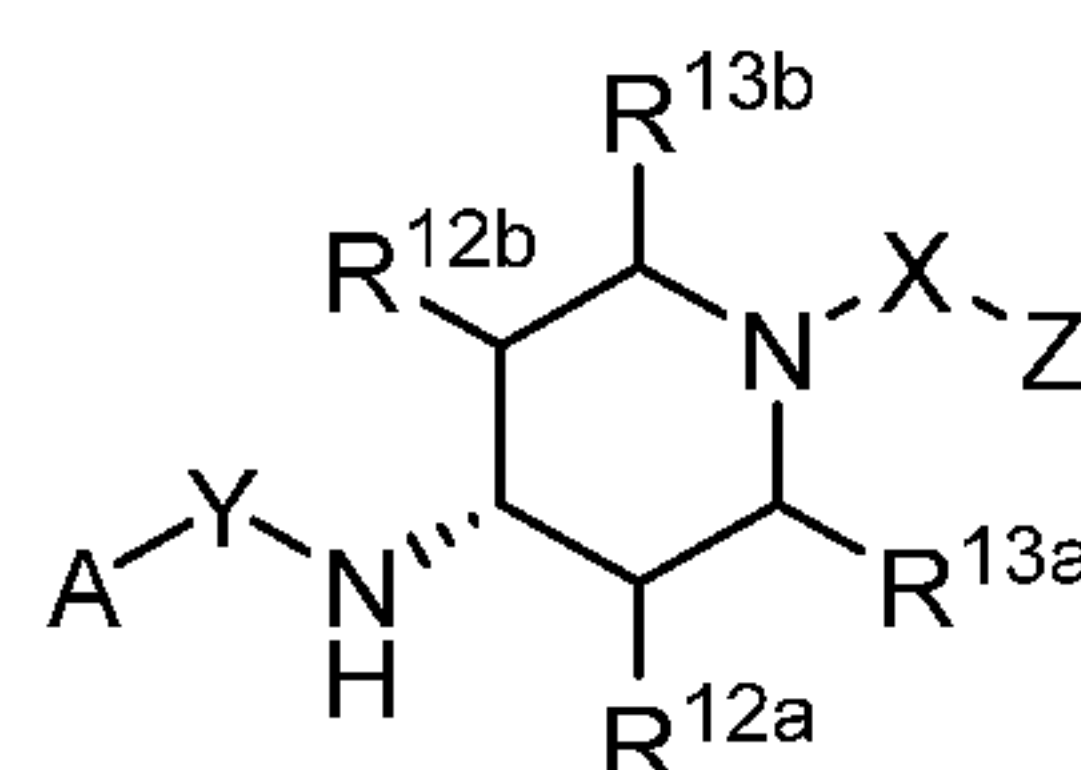
[0053] In another embodiment, Compounds of the Disclosure are compounds having Formula III, Formula IV, or Formula V:

**III****IV****V**

and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein R^{10a}, R^{10b}, R^{11a}, and R^{11b} are each independently selected from the group consisting of hydrogen and C₁₋₄ alkyl; and A, Y, X, and Z are as defined above in connection with Formula I. In another embodiment, X is -N(R³)C(=O)- and Z is (amino)alkyl. In another embodiment, X is -N(R³)- and Z is hydrogen.

[0054] In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is optionally substituted 4- to 14-membered heterocyclenyl.

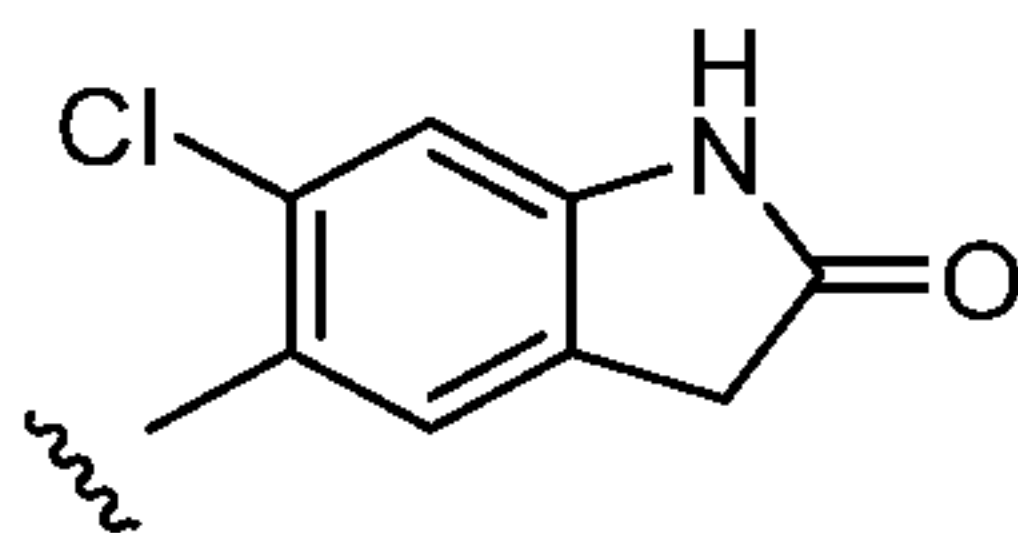
[0055] In another embodiment, Compounds of the Disclosure are compounds having Formula VI, Formula VII, or Formula VIII:

**VI****VII****VIII**

and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein R^{12a}, R^{12b}, R^{13a}, and R^{13b} are each independently selected from the group consisting of hydrogen and C₁₋₄ alkyl; and A, Y, X, and Z are as defined above in connection with

Formula I. In another embodiment, X is selected from the group consisting of $-\text{C}(=\text{O})\text{C}(\text{R}^4)(\text{H})-$, $-\text{C}(=\text{O})-$, and $-\text{S}(=\text{O})_2-$; and R^4 is selected from the group consisting of hydrogen and amino. In another embodiment, Z is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, aralkyl, and (hetaroaryl)alkyl.

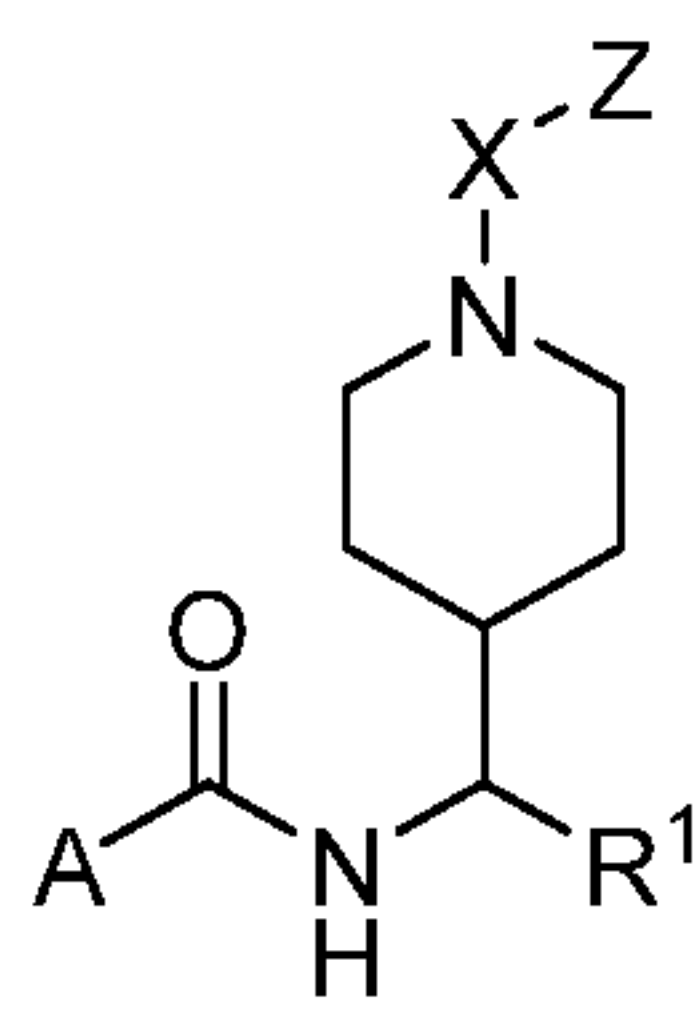
[0056] In another embodiment, Compounds of the Disclosure are compounds having Formula VI, Formula VII, or Formula VIII, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein R^{12a} , R^{12b} , R^{13a} , and R^{13b} are each independently selected from the group consisting of hydrogen and C_{1-4} alkyl; A is 5-indolinyl-2-one that is optionally substituted with one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, C_{1-6} alkyl, haloalkyl, and hydroxyalkyl; Y is $-\text{C}(=\text{O})-$; X is $-\text{S}(=\text{O})_2-$; and Z is as defined above in connection with Formula I. In another embodiment, A is 6-chloro-5-indolinyl-2-one, *i.e.*,



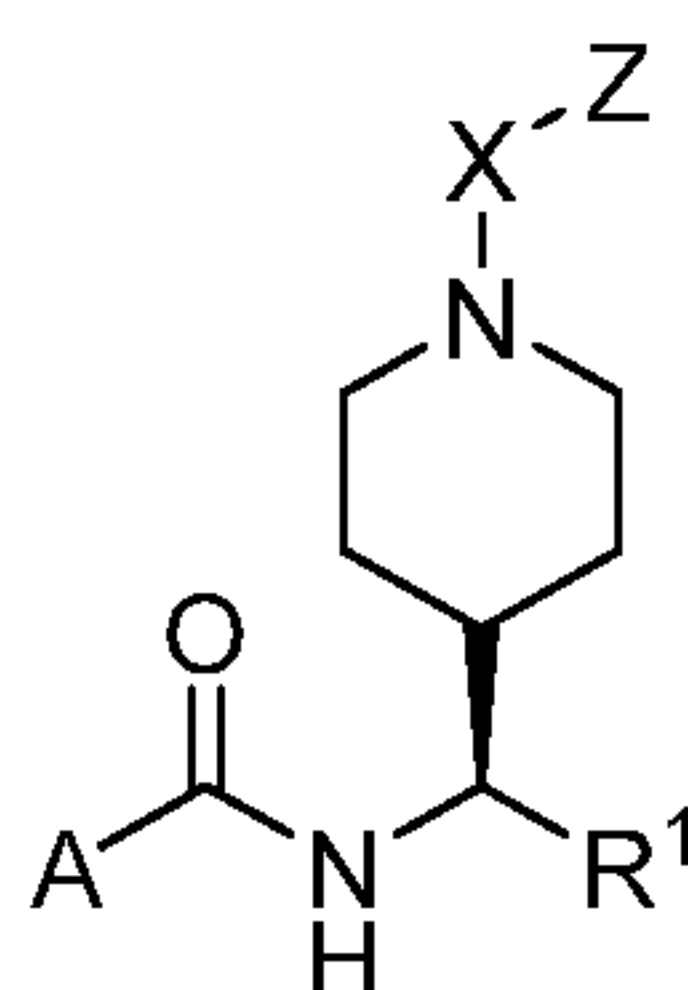
In another embodiment, Z is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, aralkyl, and (hetaroaryl)alkyl.

[0057] In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is $-\text{C}(\text{H})\text{R}^1\text{R}^2$. In this embodiment, a hydrogen atom of R^1 and R^2 is replaced with $-\text{X}-\text{Z}$.

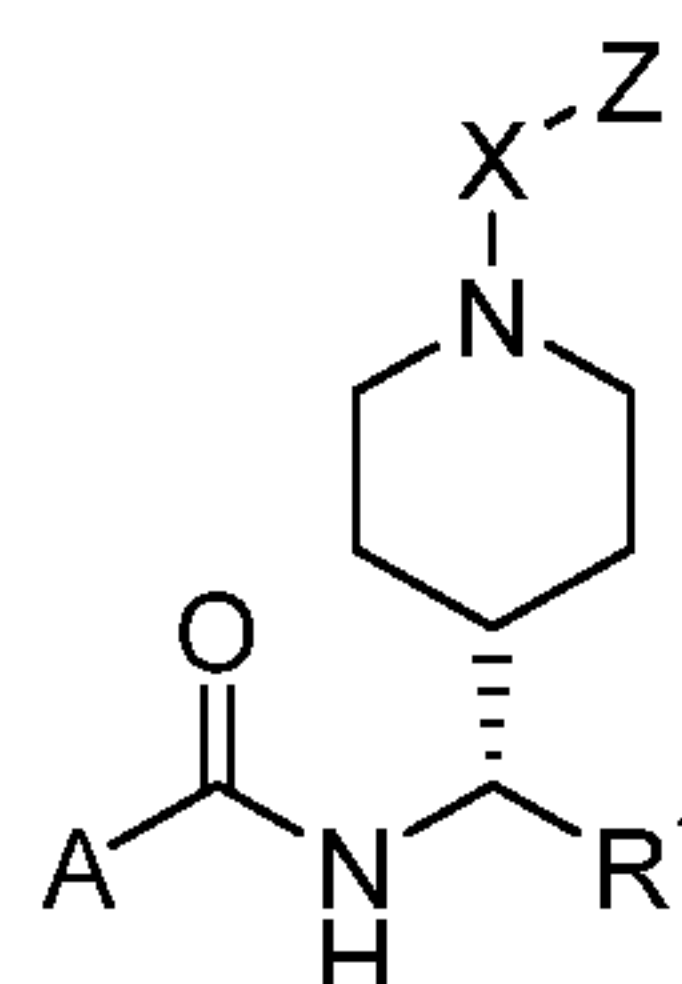
[0058] In another embodiment, Compounds of the Disclosure are compounds having Formula IX, Formula X, or Formula XI:



IX



X



XI

and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof. In another embodiment, R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, alkoxy carbonyl, and optionally substituted C_{6-14} aryl. In another embodiment, R^1 is selected from the group consisting of hydrogen and methyl. In another embodiment, X is $-C(=O)C(R^4)(H)-$ and R^4 is amino. In another embodiment, X is selected from the group consisting of:



In another embodiment, Z is C_{1-6} alkyl. In another embodiment, Z is methyl.

[0059] In another embodiment, Compounds of the Disclosure are compounds having any one of Formula **I-XI**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Y is $-C(R^{5a})(R^{5b})C(=O)-$. In another embodiment, R^{5a} and R^{5b} are each independently selected from the group consisting of hydrogen and methyl.

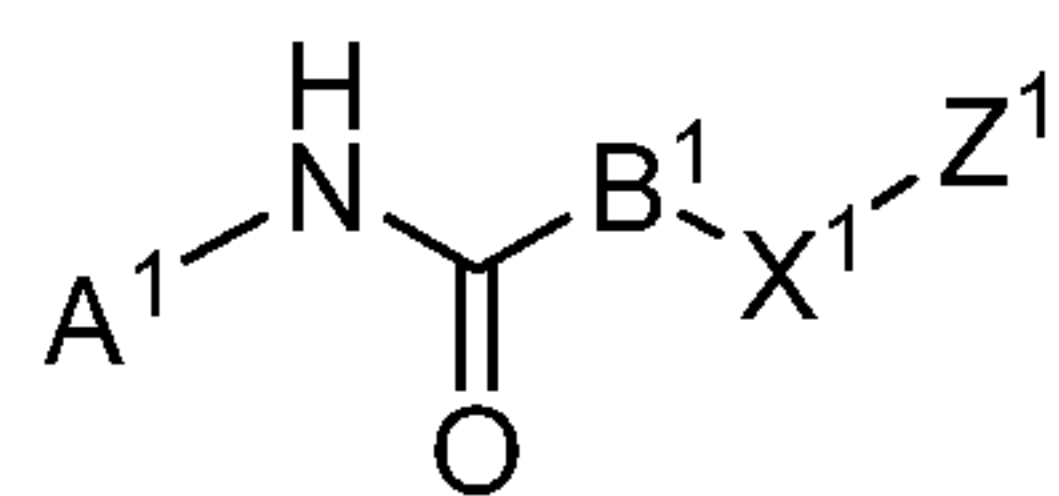
[0060] In another embodiment, Compounds of the Disclosure are compounds having any one of Formula **I-XI**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Y is $-S(=O)_2-$.

[0061] In another embodiment, Compounds of the Disclosure are compounds having any one of Formula **I-XI**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Y is $-C(=O)-$.

[0062] In another embodiment, Compounds of the Disclosure are compounds having any one of Formula **I-XI**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein A is selected from the group consisting of 1,2,3-triazolyl, 1,2,4-triazolyl, 2-(1,2,3,4-tetrahydroquinolinyl), 2-indolyl, 2-thiazolyl, 3-(1,2,4-oxadiazolyl), 3-isothiazolyl, 5-(1,3-dihydro-2H-benzo[d]imidazolyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-b]pyridinyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-c]pyridinyl-2-one), 5-(2,2-difluorobenzo[d][1,3]dioxolyl), 5-benzo[d]oxazolyl-2(3H)-one, 5-indolinyl-2-one, 6-benzo[b][1,4]oxazinyl-3-one, and 6-isoquinolinyl.

[0063] In another embodiment, Compounds of the Disclosure are compounds having any one of Formula **I-XI**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein A is 5-indolinyl-2-one.

[0064] In another embodiment, Compounds of the Disclosure are compounds having Formula **XII**:



and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein:

[0065] A^1 is selected from the group consisting of 1,2,3-triazolyl, 1,2,4-triazolyl, 1-imidazolyl, 1-isoquinolyl, 1-pyrazolyl, 2-(1,2,3,4-tetrahydroquinolyl), 2-benzo[d]imidazolyl, 2-benzo[d]thiazolyl, 2-chromenyl-4-one, 2-furanyl, 2-imidazo[1,2-b]pyridazinyl, 2-imidazolyl, 2-indolyl, 2-naphthalenyl, 2-pyrazinyl, 2-pyridyl, 2-pyrimidinyl, 2-pyrrolidinyl, 2-pyrrolyl, 2-quinolyl, 2-quinoxalyl, 2-thiazolo[5,4-c]pyridinyl, 2-thiazolyl, 2-thiophenyl, 3-(1,2,3,4-tetrahydroisoquinoline), 3-(1,2,4-oxadiazolyl), 3-imidazo[1,2-a]pyrimidinyl, 3-indazolyl, 3-indolyl, 3-isothiazolyl, 3-pyrazolyl, 3-pyridazinyl, 3-pyridinyl-2-one, 3-pyridyl, 3-pyrrolo[3,2-b]pyridinyl, 3-quinolyl, 4-(2,2-difluorobenzo[d][1,3]dioxolyl), 4-cyclohexanyl-1-amine, 4-imidazolyl, 4-indolyl-2-one, 4-indolyl, 4-isothiazolyl, 4-oxazolyl, 4-piperidinyl, 4-pyrazolyl, 4-pyridyl, 4-quinolyl, 5-(1,3-dihydro-2H-benzo[d]imidazolyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-b]pyridinyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-c]pyridinyl-2-one), 5-(2,2-difluorobenzo[d][1,3]dioxolyl), 5-(2,4-dihydro-3H-1,2,4-triazolyl-3-one), 5-4H-furo[3,2-b]pyrrolyl, 5-benzo[c][1,2,5]oxadiazolyl, 5-benzo[d][1,3]dioxolyl, 5-benzo[d]oxazolyl-2(3H)-one, 5-bicyclo[2.2.1]heptyl-2-ene, 5-indolyl-2,3-dione, 5-indolyl-2-one, 5-indolyl, 5-isoindolyl-1-one, 5-isoxazolyl, 5-pyrazolo[3,4-c]pyridinyl, 5-pyrazolyl, 5-pyrimidinyl, 5-thiazolyl, 6-(1,2,3,4-tetrahydronaphthalenyl), 6-(3,4-dihydroquinolyl-2(1H)-one), 6-(3,4-dihydroquinoxalyl-2(1H)-one), 6-(4,5-dihydropyridazinyl-3(2H)-one), 6-benzo[b][1,4]oxazinyl-3-one, 6-benzo[d]imidazolyl, 6-benzo[d]oxazolyl-2(3H)-one, 6-benzo[d]thiazolyl, 6-chromenyl-2-one, 6-imidazo[2,1-b]thiazole, 6-indazolyl, 6-indolyl-2-one, 6-indolyl, 6-isoquinolyl, 6-quinolyl, 6-quinoxalyl, 6-quinoxalyl-2(1H)-one, 7-(3,4-dihydroquinolyl-2(1H)-one), 7-(3,4-dihydroquinoxalin-2(1H)-one), 7-benzo[b][1,4]oxazinyl-3-one, 7-indolyl-2-one, 7-quinolyl, 8-benzo[b][1,4]oxazinyl-3-one, cyclopropanyl, phenyl, 4-(prop-1-en-1-yl)-imidazole, 1-butanyl-imidazole, sec-butylcyclopropane, 2-(ethylsulfonyl)propanyl, 1-isobutylpyrrolidine, 4-pyridyl 1-oxide, and 5-benzo[c][1,2,5]oxadiazolyl 1-oxide,

[0066] each of which is optionally substituted with one, two, or three substituents independently selected from the group consisting of halo, hydroxy, alkoxy, amino,

alkylamino, dialkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, C₁₋₆ alkyl, haloalkyl, hydroxyalkyl, (carboxamido)alkyl, (cycloalkyl)alkyl, optionally substituted C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 5- to 14-membered heteroaryl, optionally substituted 4- to 14-membered heterocyclo, and aralkyl;

[0067] B¹ is selected from the group consisting of optionally substituted C₃₋₁₂ cycloalkylenyl and optionally substituted 4- to 14-membered heterocyclenyl;

[0068] X¹ is selected from the group consisting of -N(R^{3a})-, -S(=O)₂-, -S(=O)₂N(R^{3a})-, -N(R^{3a})S(=O)₂-, -S(=O)₂C(R^{4a})(H)-, -C(=O)-, -C(=O)N(R^{3a})-, -N(R^{3a})C(=O)-, -C(=O)O-, -OC(=O)-, -C(=O)C(R^{4a})(H)N(R^{3a})-, -N(R^{3a})C(=O)C(R^{4a})(H)-, and -C(=O)C(R^{4a})(H)-; or X¹ is absent, i.e., Z¹ forms a bond with B¹;

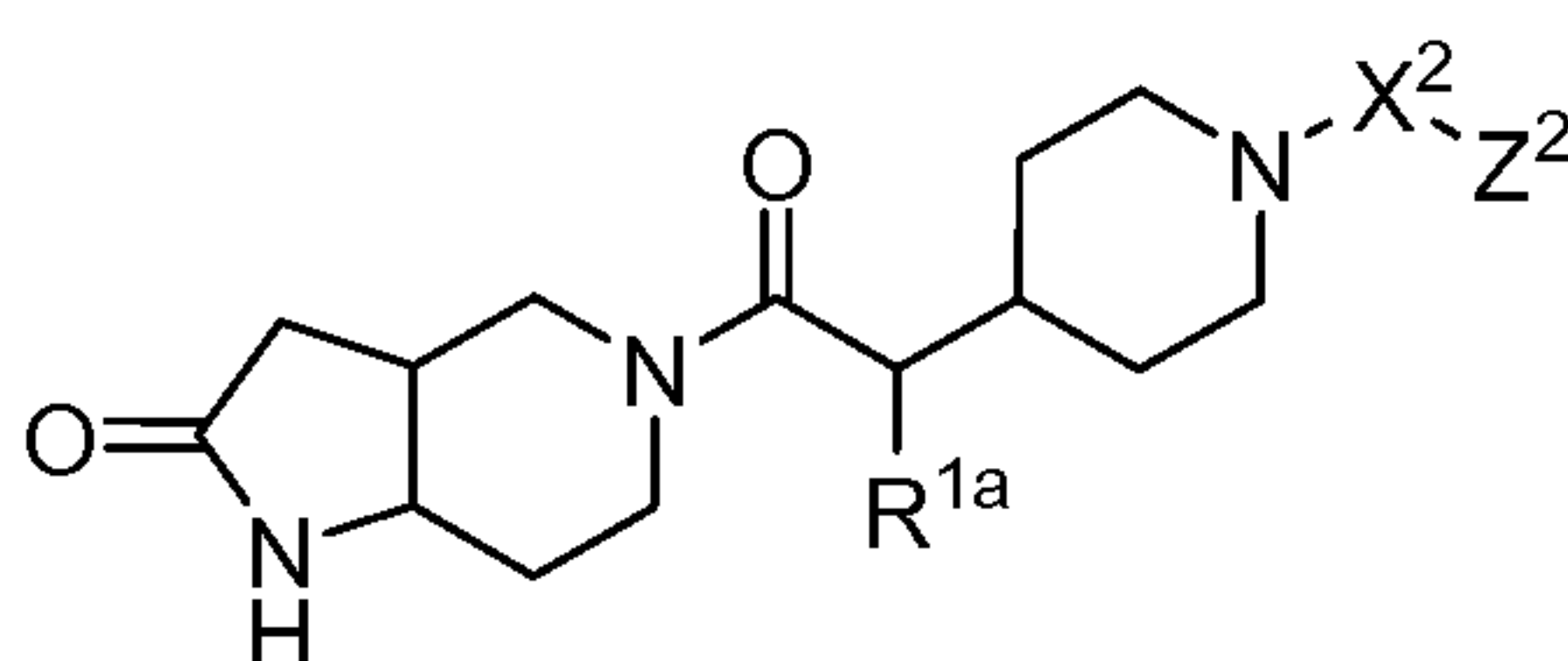
[0069] Z¹ is selected from the group consisting of hydrogen, optionally substituted C₁₋₆ alkyl, fluoroalkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, (cycloalkyl)alkyl, (amino)(hydroxy)alkyl, (amino)(aryl)alkyl, (hydroxy)(aryl)alkyl, (aralkylamino)alkyl, (hydroxyalkylamino)alkyl, alkoxyalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C₃₋₁₂ cycloalkyl, aralkyl, and (heteroaryl)alkyl;

[0070] R^{3a} is selected from the group consisting of hydrogen and C₁₋₄ alkyl; and

[0071] R^{4a} is selected from the group consisting of hydrogen, C₁₋₄ alkyl, hydroxy, amino, alkylamino, and dialkylamino.

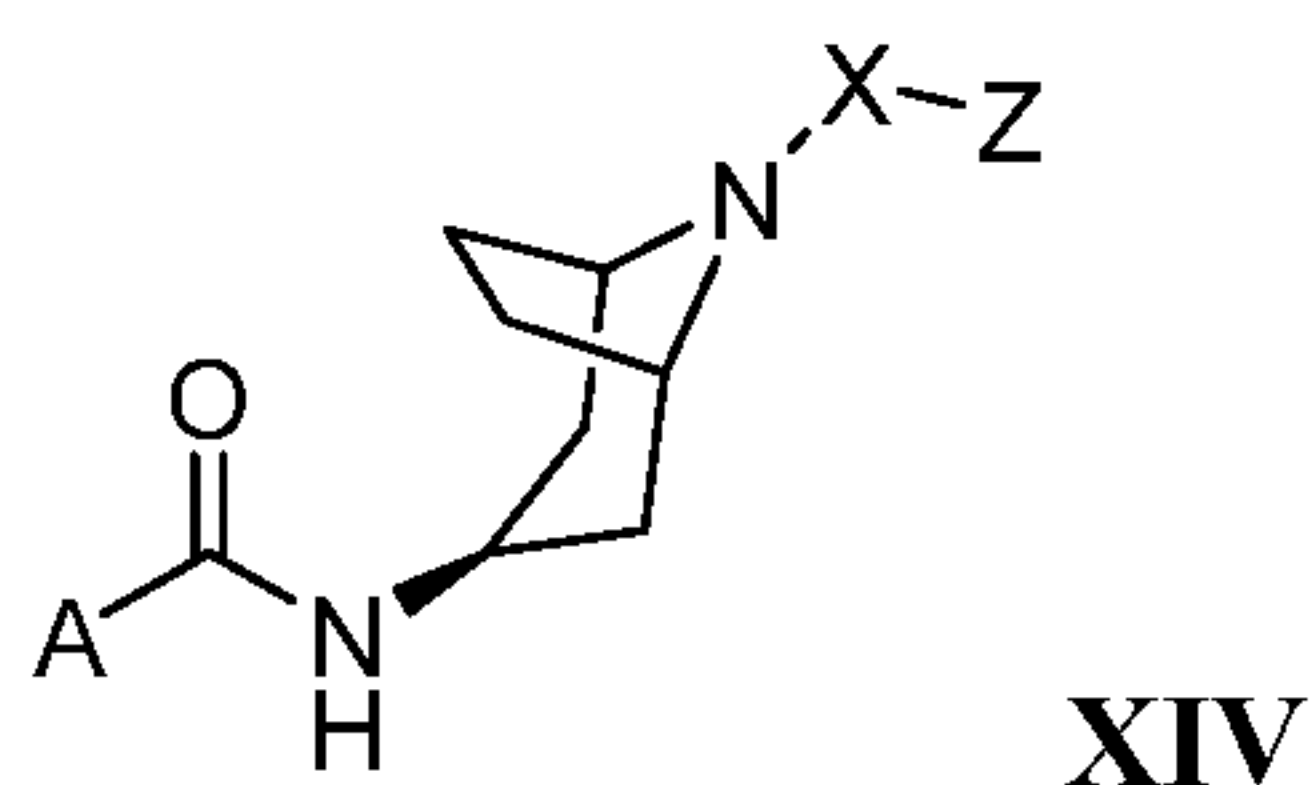
[0072] In another embodiment, Compounds of the Disclosure are compounds having Formula **XII**, or a pharmaceutically acceptable salt or hydrate thereof, wherein A¹ is 5-indolinyl-2-one. In another embodiment, B¹ is optionally substituted C₃₋₁₂ cycloalkylenyl. In another embodiment, X¹ is selected from the group consisting of -S(=O)₂- and -C(=O)-. In another embodiment, Z¹ is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, and (dialkylamino)alkyl.

[0073] In another embodiment, Compounds of the Disclosure are compounds having Formula **XIII**:

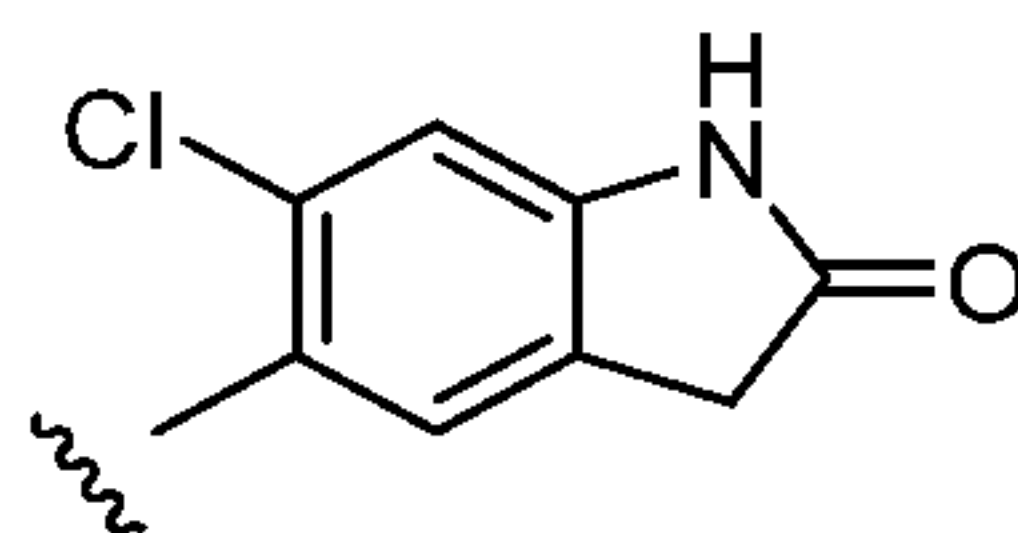


or a pharmaceutically acceptable salt or hydrate thereof, wherein

- [0074] X^2 is selected from the group consisting of $-N(R^{3b})-$, $-S(=O)_2-$, $-S(=O)_2N(R^{3b})-$, $-N(R^{3b})S(=O)_2-$, $-S(=O)_2C(R^{4b})(H)-$, $-C(=O)-$, $-C(=O)N(R^{3b})-$, $-N(R^{3b})C(=O)-$, $-C(=O)O-$, $-OC(=O)-$, $-C(=O)C(R^{4b})(H)N(R^{3b})-$, $-N(R^{3b})C(=O)C(R^{4b})(H)-$, and $-C(=O)C(R^{4b})(H)-$; or X is absent, i.e., Z^2 forms a bond with the nitrogen atom;
- [0075] Z^2 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, fluoroalkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, (cycloalkyl)alkyl, (amino)(hydroxy)alkyl, (amino)(aryl)alkyl, (hydroxy)(aryl)alkyl, (aralkylamino)alkyl, (hydroxyalkylamino)alkyl, alkoxyalkyl, optionally substituted C_{6-14} aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl optionally substituted C_{3-12} cycloalkyl, aralkyl, and (heteroaryl)alkyl;
- [0076] R^{1a} is selected from the group consisting of hydrogen, C_{1-6} alkyl, and optionally substituted C_{6-14} aryl;
- [0077] R^{3b} is selected from the group consisting of hydrogen and C_{1-4} alkyl; and
- [0078] R^{4b} is selected from the group consisting of hydrogen, C_{1-4} alkyl, hydroxy, amino, alkylamino, and dialkylamino.
- [0079] In another embodiment, Compounds of the Disclosure are compounds having Formula **XIII**, or a pharmaceutically acceptable salt or hydrate thereof, wherein X^2 is selected from the group consisting of $-S(=O)_2-$ and $-C(=O)-$. In another embodiment, Z^2 is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, and (dialkylamino)alkyl. In another embodiment, X^2 is absent; and Z^2 is hydrogen. In another embodiment, R^{1a} is selected from the group consisting of hydrogen and methyl.
- [0080] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Y is $-C(=O)-$ and A is selected from the group consisting of 5-indolinyl-2-one and 1,2,3-triazolyl.
- [0081] In another embodiment, Compounds of the Disclosure are compounds having Formula **XIV**:

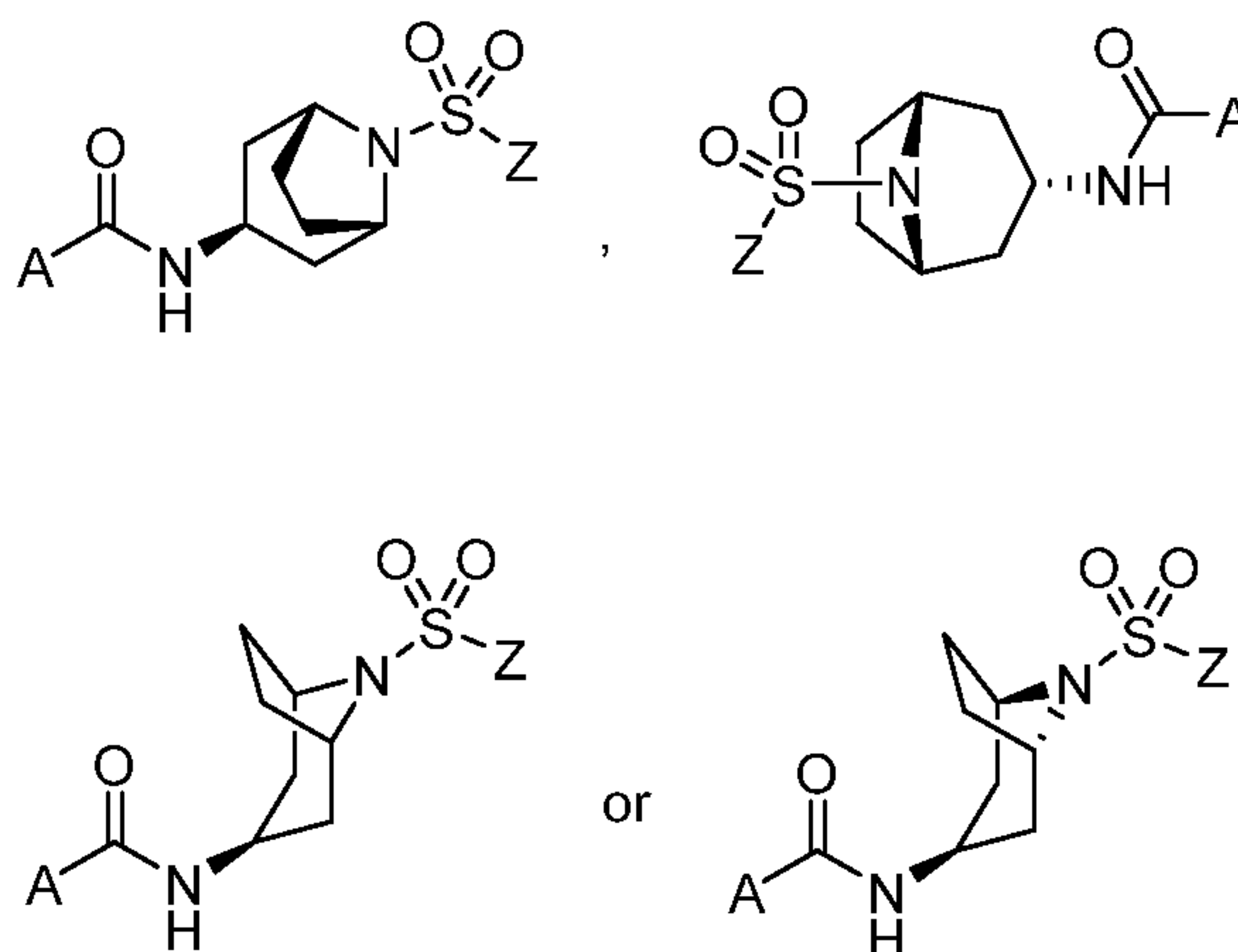


and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein A, X, and Z are as defined above in connection with Formula I. In another embodiment, X is selected from the group consisting of S(=O)_2^- and $-\text{S(=O)}_2\text{C(R}^4\text{)(H)-}$. In another embodiment, X is $-\text{S(=O)}_2^-$. In another embodiment, X is $-\text{S(=O)}_2\text{CH}_2^-$. In another embodiment, Z is selected from the group consisting of optionally substituted C_{6-14} aryl, optionally substituted 4- to 14-membered heterocyclo, and optionally substituted C_{3-12} cycloalkyl. In another embodiment, Z is optionally substituted 4- to 14-membered heterocyclo. In another embodiment, Z is an optionally substituted piperidinyl, wherein the nitrogen atom is attached to X or the 4-carbon atom is attached to X. In another embodiment, A is 5-indoliny-2-one that is optionally substituted with one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, C_{1-6} alkyl, haloalkyl, and hydroxyalkyl. In another embodiment, A is 6-chloro-5-indoliny-2-one, *i.e.*,



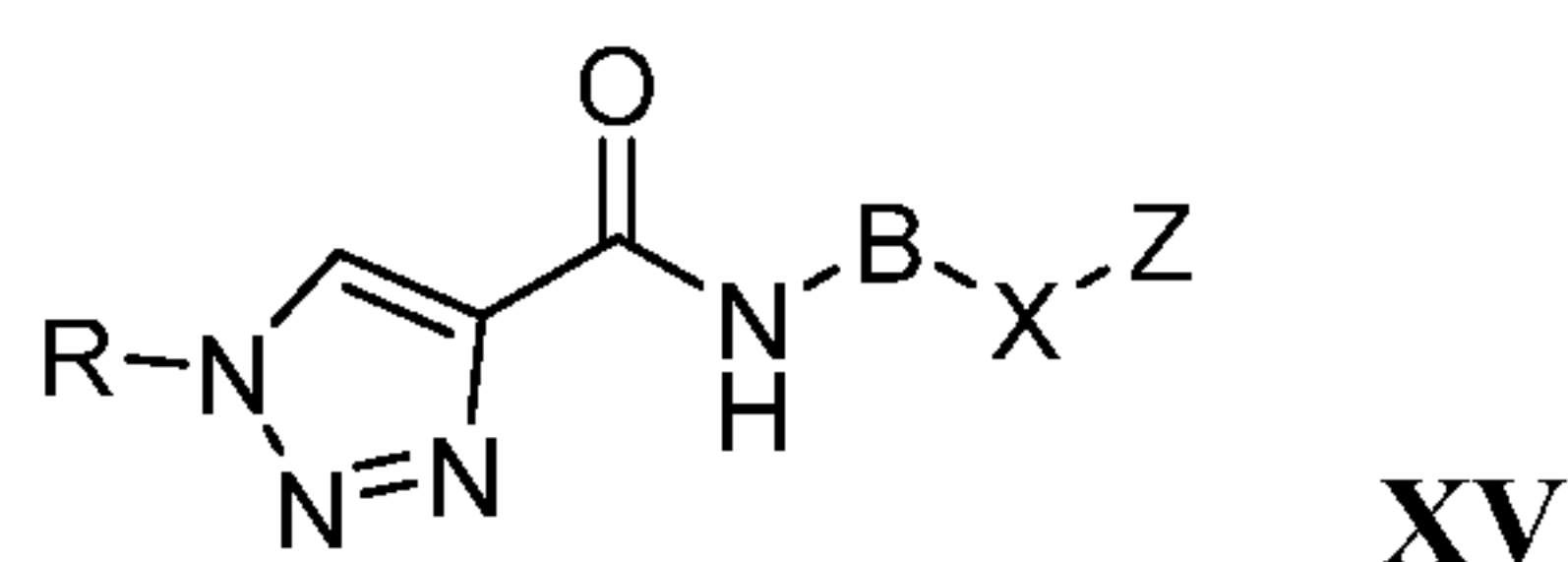
In another embodiment, a Compound of the Disclosure is N-((1R,3r,5S)-8-((4-(benzylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-chloro-2-oxoindoline-5-carboxamide or 6-chloro-2-oxo-N-((1R,3r,5S)-8-(((1-(4,4,4-trifluorobutyl)piperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)indoline-5-carboxamide, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof.

[0082] It will be understood by those of ordinary skill in the art that compounds having Formula XIV can be drawn in various ways, *e.g.*,



[0083] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein A is 1,2,3-triazolyl which may be optionally substituted with one substituent, and Y is -C(=O)-.

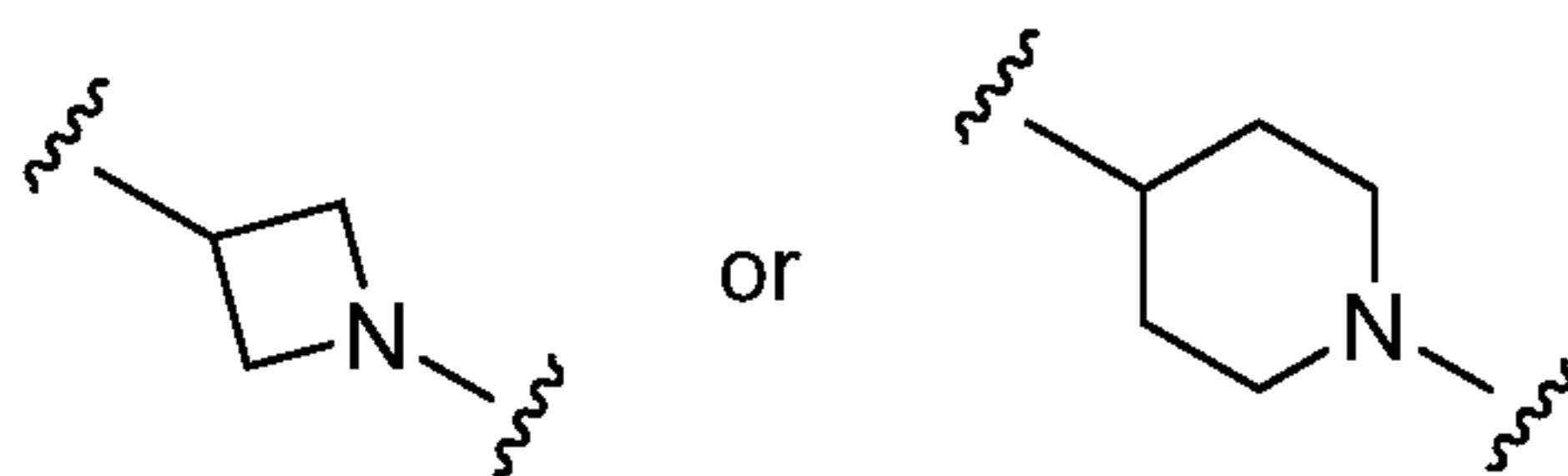
[0084] In another embodiment, Compounds of the Disclosure are compounds having having Formula **XV**:



and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein:

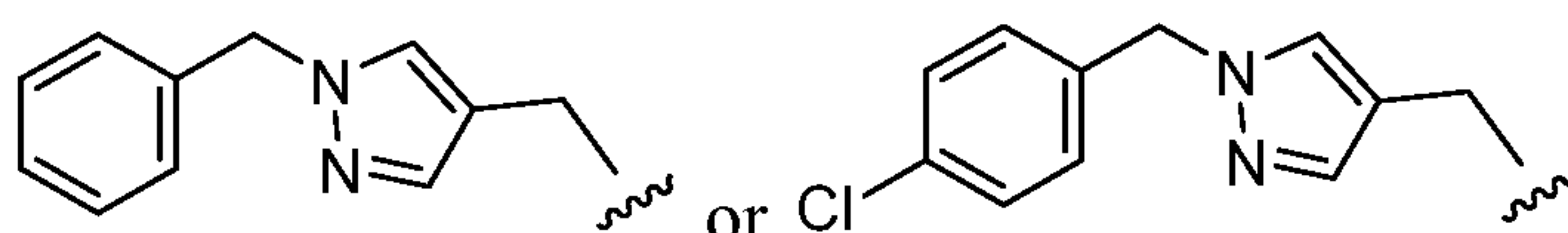
[0085] R is selected from the group consisting of C₁₋₆ alkyl and C₃₋₁₂ cycloalkyl;

[0086] B is optionally substituted 4- or 6- to 14-membered heterocyclenyl, *e.g.*, B is:

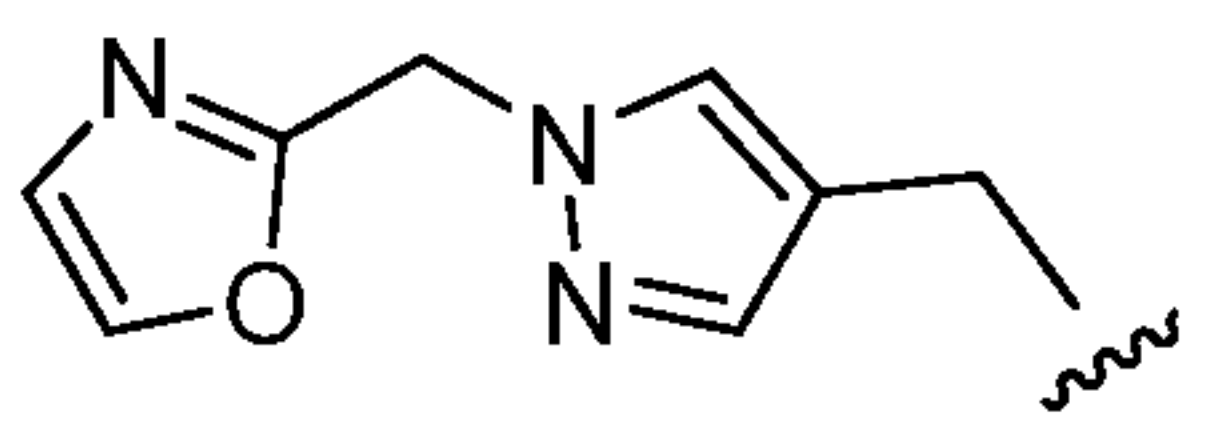


(wherein the nitrogen atom is attached to -X-Z); and

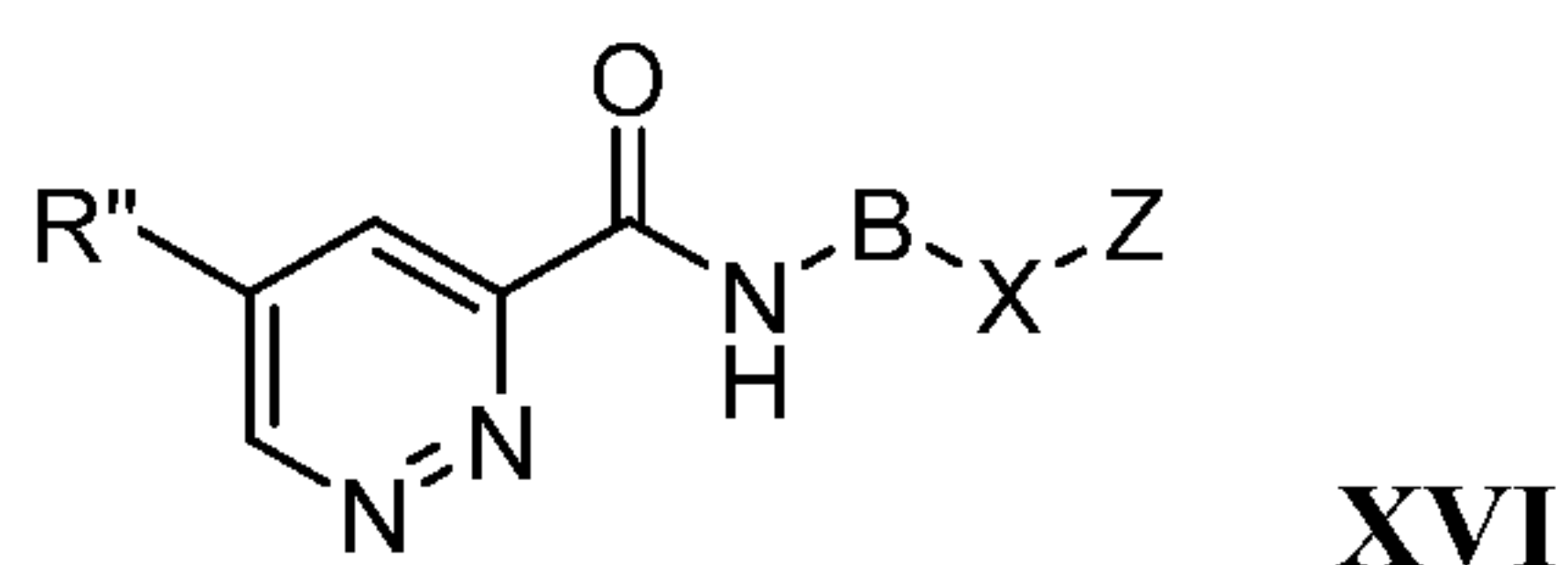
[0087] X and Z are as defined above in connection with Formula **I**. In another embodiment, X is absent. In another embodiment, Z is selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₃₋₁₂ cycloalkyl, aralkyl, and (heteroaryl)alkyl, or Z is -CH(R^{9a})(R^{9b}). In another embodiment, Z is selected from the group consisting of aralkyl and (heteroaryl)alkyl. In another embodiment, Z is (heteroaryl)alkyl that is substituted with an aralkyl, *e.g.*,



or (heteroaryl)alkyl, *e.g.*,



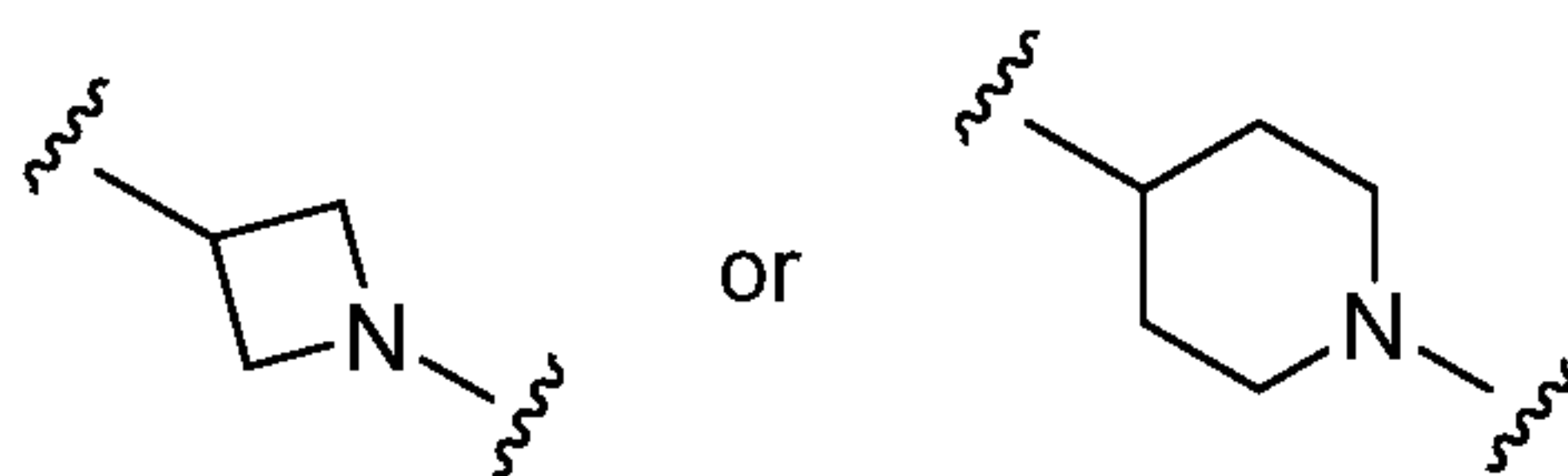
[0088] In another embodiment, Compounds of the Disclosure are compounds having having Formula **XVI**:



and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein:

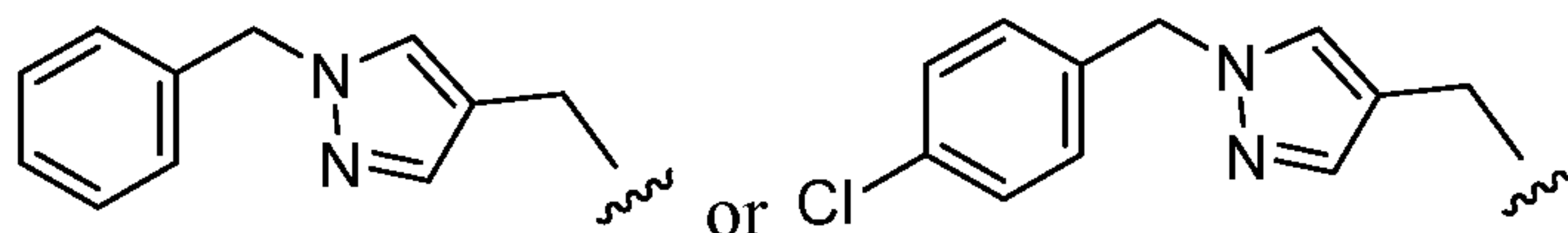
[0089] R" is selected from the group consisting of C₁₋₆ alkyl and C₃₋₁₂ cycloalkyl;

[0090] B is optionally substituted 4- or 6- to 14-membered heterocyclenyl, *e.g.*, B is:

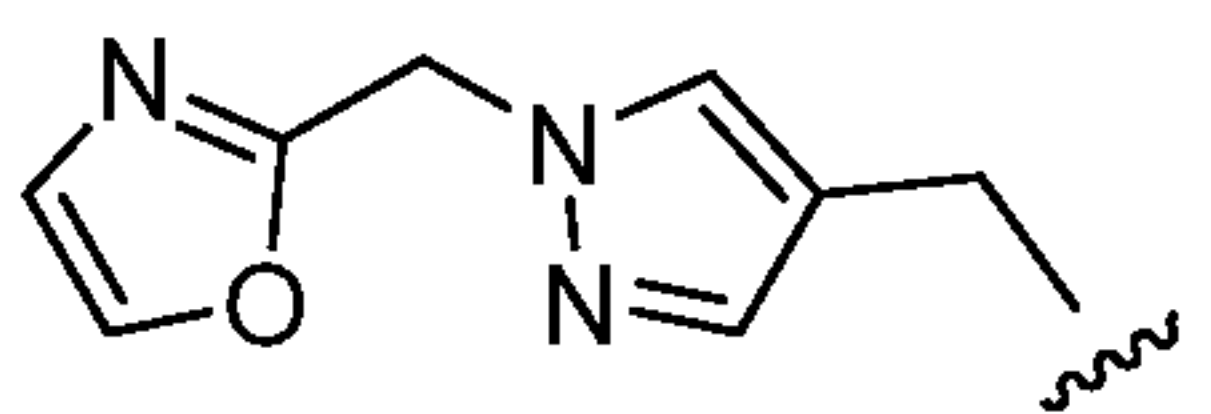


(wherein the nitrogen atom is attached to -X-Z); and

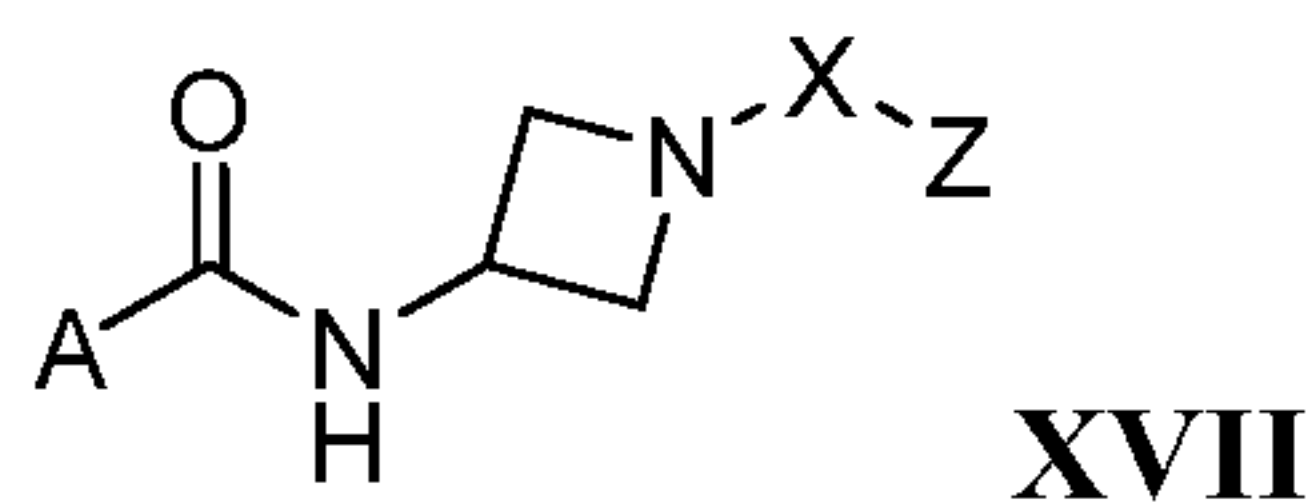
[0091] X and Z are as defined above in connection with Formula I. In another embodiment, X is absent. In another embodiment, Z is selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₃₋₁₂ cycloalkyl, aralkyl, and (heteroaryl)alkyl, or Z is -CH(R^{9a})(R^{9b}). In another embodiment, Z is selected from the group consisting of aralkyl and (heteroaryl)alkyl. In another embodiment, Z is (heteroaryl)alkyl that is substituted with an aralkyl, *e.g.*,



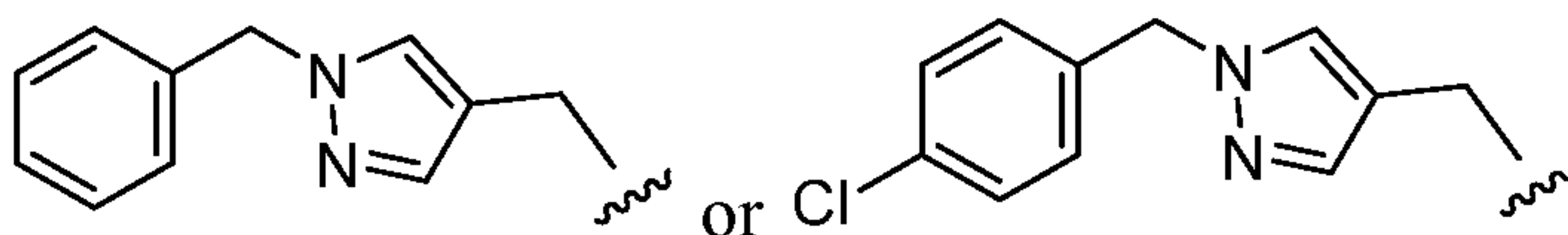
or (heteroaryl)alkyl, *e.g.*,



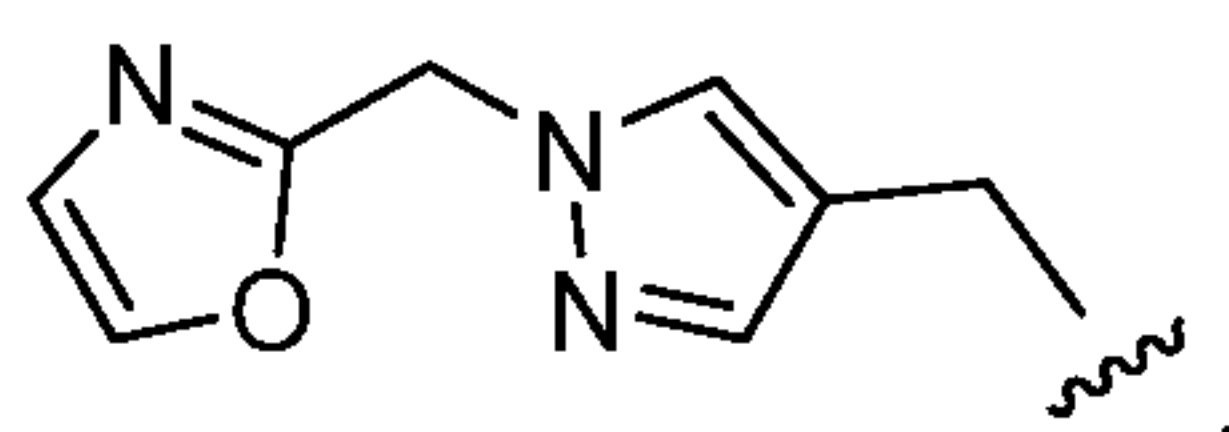
[0092] In another embodiment, Compounds of the Disclosure are compounds having having Formula XVII:



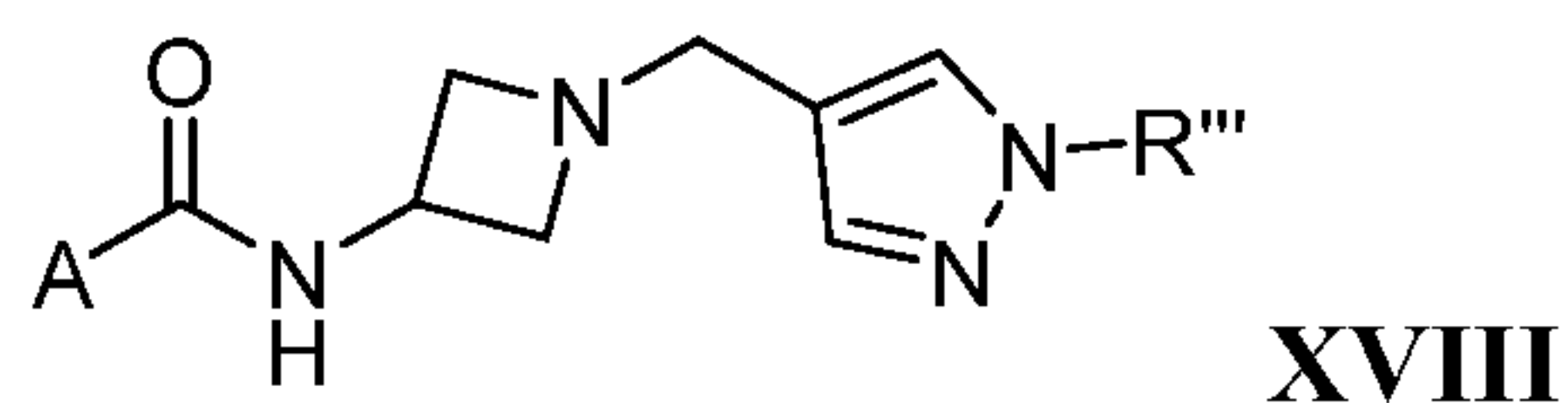
and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein A, X, and Z are as defined above in connection with Formula I. In another embodiment, X is absent. In another embodiment, Z is selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₃₋₁₂ cycloalkyl, aralkyl, and (heteroaryl)alkyl, or Z is -CH(R^{9a})(R^{9b}). In another embodiment, Z is selected from the group consisting of aralkyl and (heteroaryl)alkyl. In another embodiment, Z is aralkyl. In another embodiment, Z is (heteroaryl)alkyl. In another embodiment, Z is (heteroaryl)alkyl that is substituted with an aralkyl, *e.g.*,



or (heteroaryl)alkyl, *e.g.*,



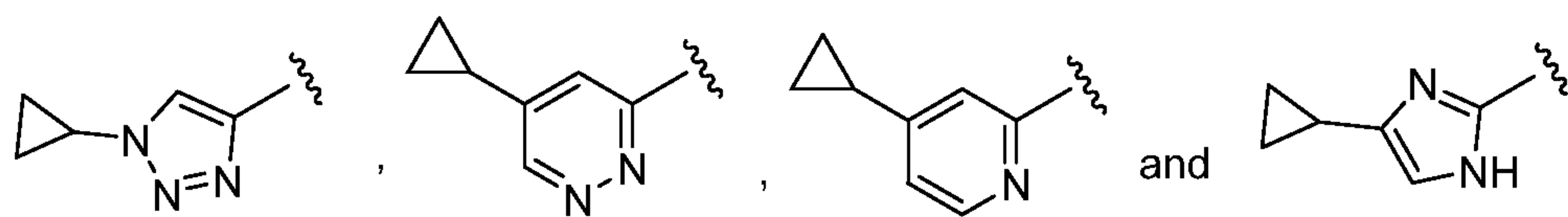
[0093] In another embodiment, Compounds of the Disclosure are compounds having having Formula **XVIII**:



and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein:

[0094] R''' is selected from the group consisting of aralkyl and (heteroaryl)alkyl; and

[0095] A is as defined above in connection with Formula I. In another embodiment, A is selected from the group consisting of 1,2,3-triazolyl, 3-pyridazinyl, 2-pyridyl, and 2-imidazolyl, each of which is optionally substituted with one substituent selected from the group consisting of C₁₋₆ alkyl and C₃₋₆ cycloalkyl. In another embodiment, A is selected from the group consisting of:



In another embodiment, R''' is aralkyl. In another embodiment, R''' is (heteroaryl)alkyl. In another embodiment, R''' is benzyl wherein the phenyl group is optionally substituted with one or two substituents, *e.g.*, -CH₂(4-Cl-Ph), -CH₂(3-Cl-Ph), and -CH₂(4-CF₃-Ph).

[0096] In another embodiment, Compounds of the Disclosure are compounds of Table 1, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, or different pharmaceutically acceptable salt thereof. The chemical names of the compounds of Table 1 are provided in Table 1A.

[0097] In another embodiment, Compounds of the Disclosure are compounds of Table 3, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, or different pharmaceutically acceptable salt thereof. The chemical names of the compounds of Table 3 are provided in Table 3A.

[0098] In another embodiment, Compounds of the Disclosure are compounds of Table 4, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, or different pharmaceutically acceptable salt thereof. The chemical names of the compounds of Table 4 are provided in Table 4A.

[0099] In another embodiment, Compounds of the Disclosure are compounds of Table 5, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, or different pharmaceutically acceptable salt thereof.

[0100] In another embodiment, Compounds of the Disclosure are compounds of Table 6, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, or different pharmaceutically acceptable salt thereof. The chemical names of the compounds of Table 6 are provided in Table 6A.

[0101] In another embodiment, Compounds of the Disclosure are compounds of Tables 1, 1A, 3, 3A, 4, 4A, 5, 6 and 6A, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, or different pharmaceutically acceptable salt thereof.

[0102] In another embodiment, Compounds of the Disclosure are compounds selected from the group consisting of:

rel-N-{1-[(1S)-1-[2-chloro-3-(2-hydroxyethoxy)phenyl]ethyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide;

N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide;

N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-4-cyclopropylpicolinamide;

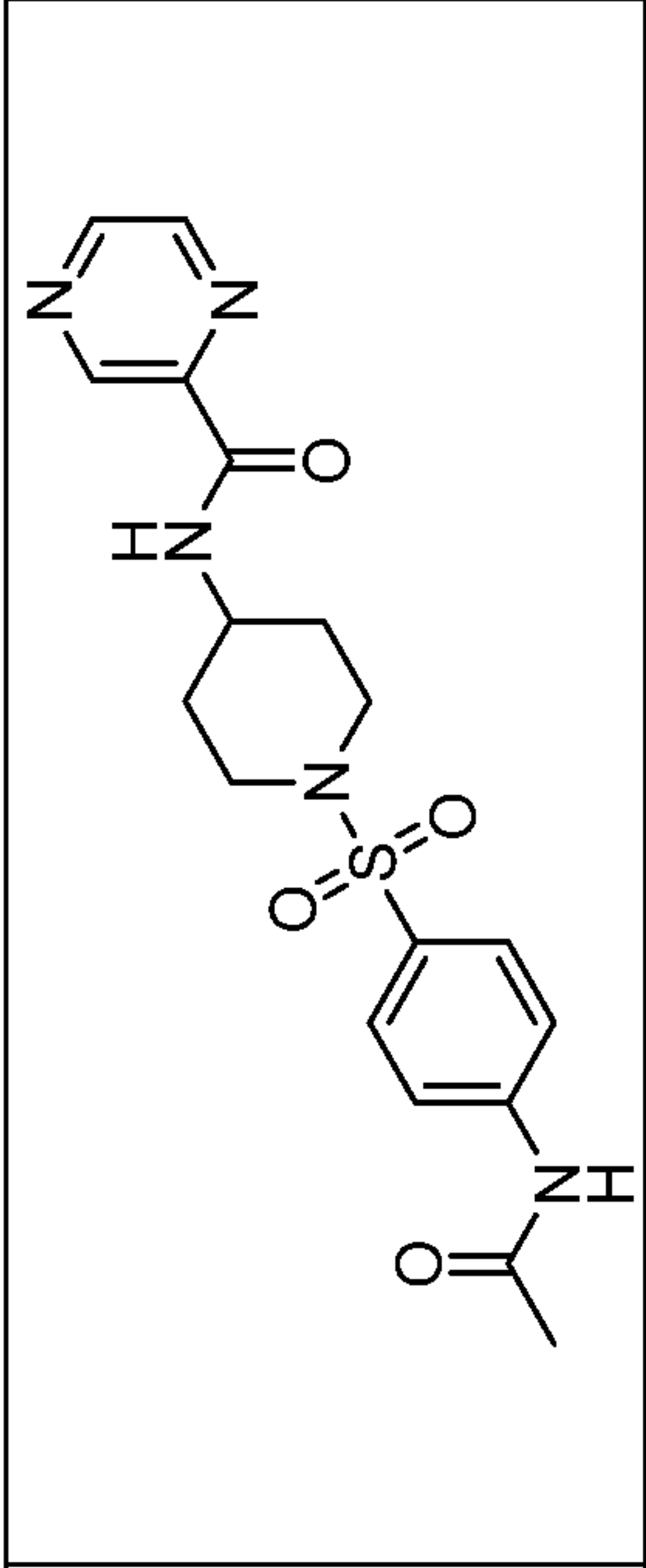
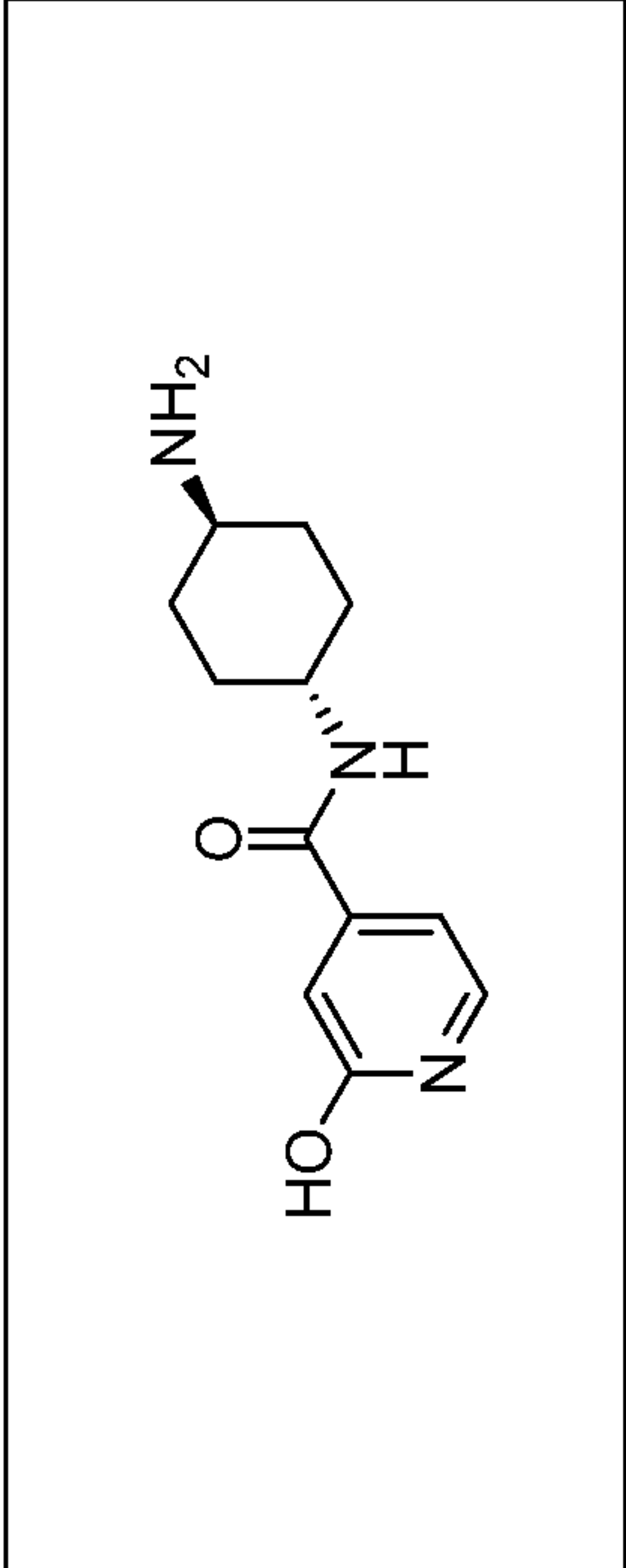
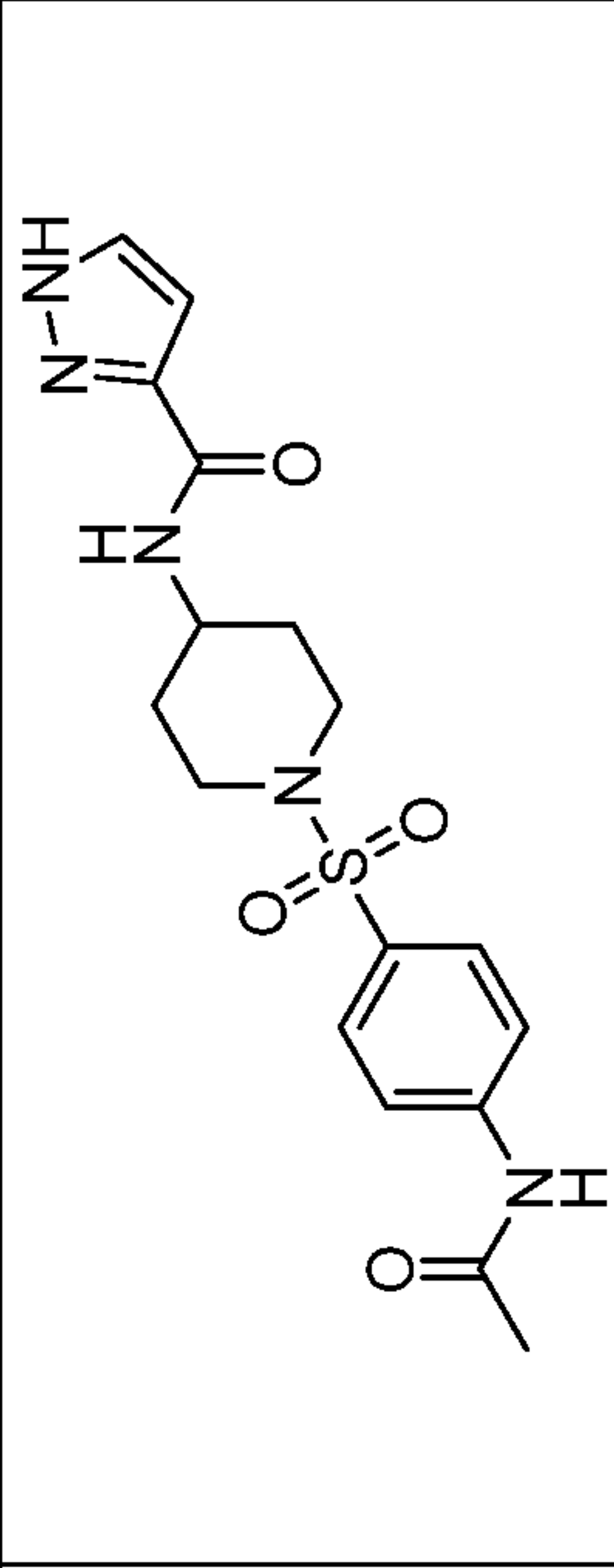
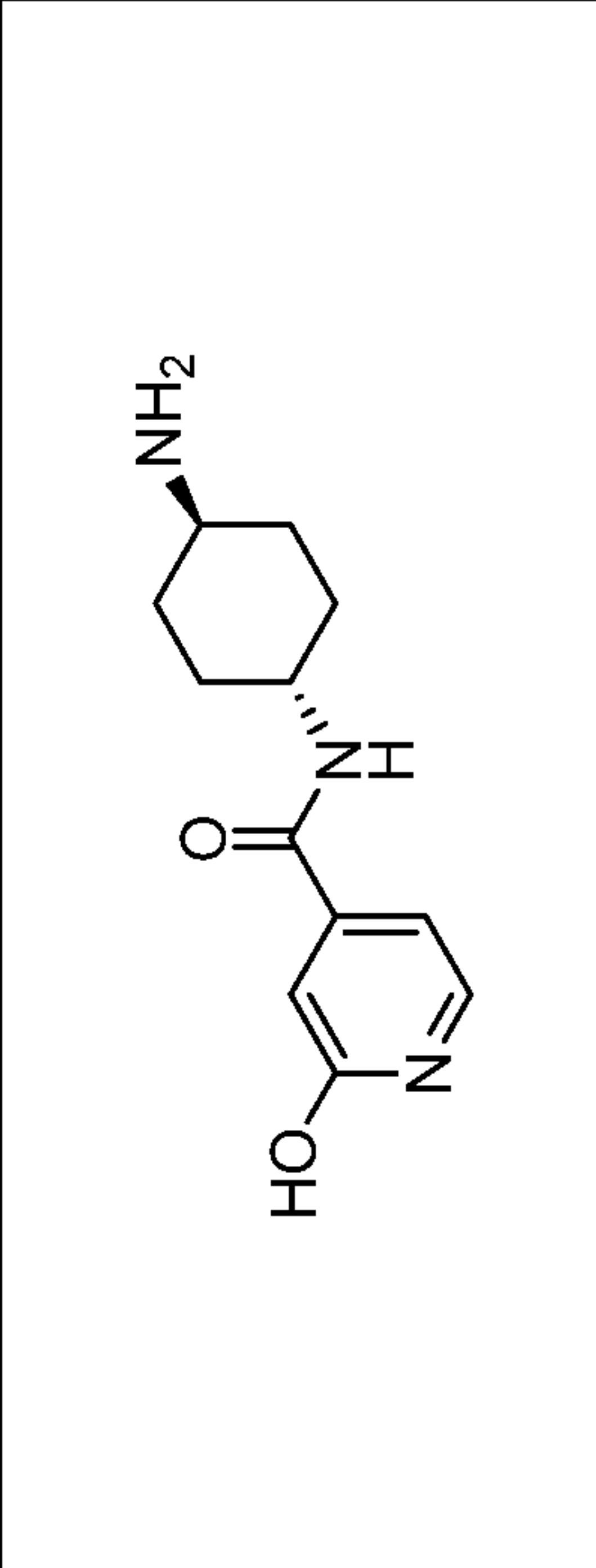
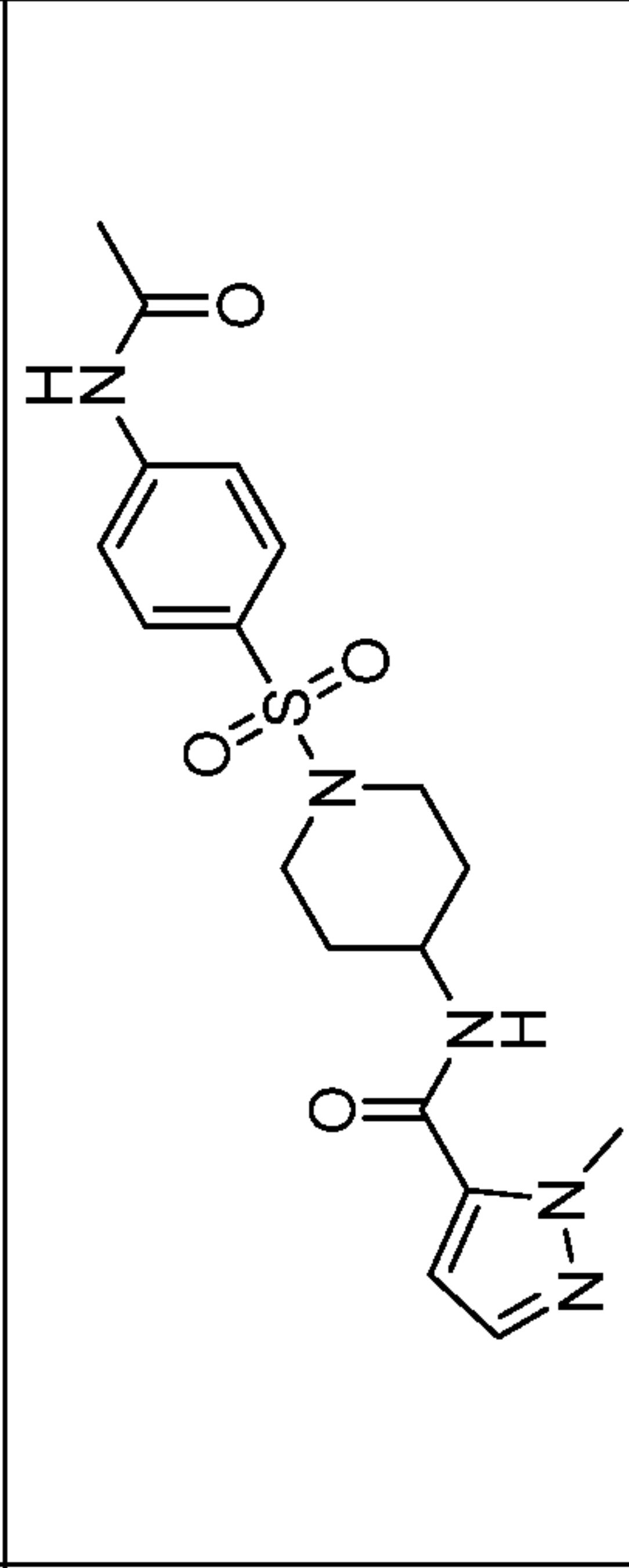
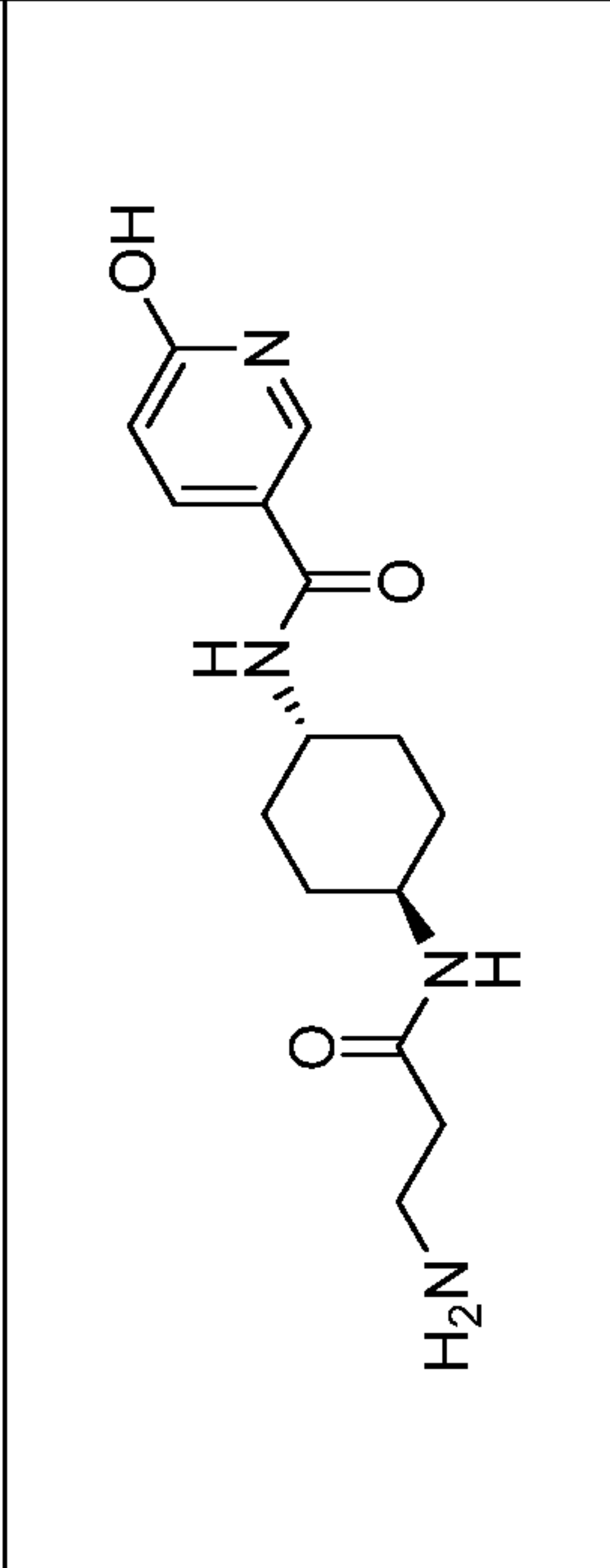
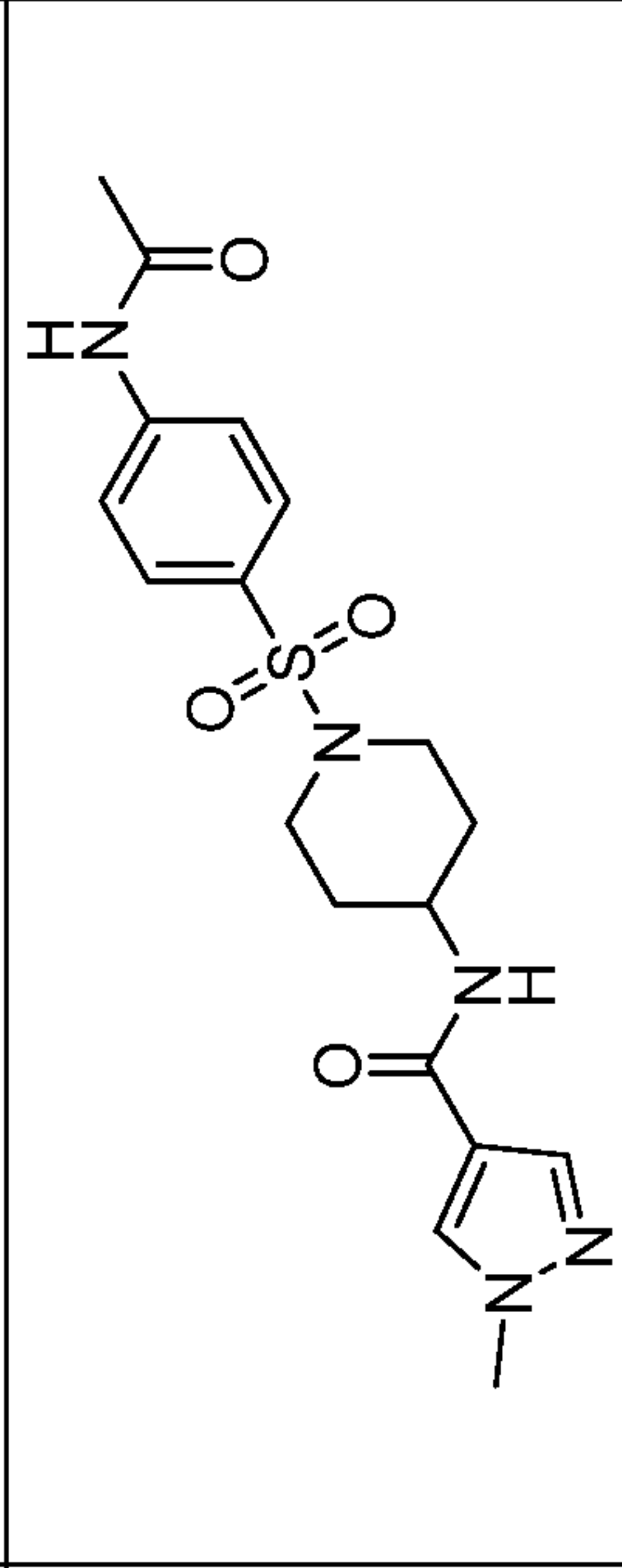
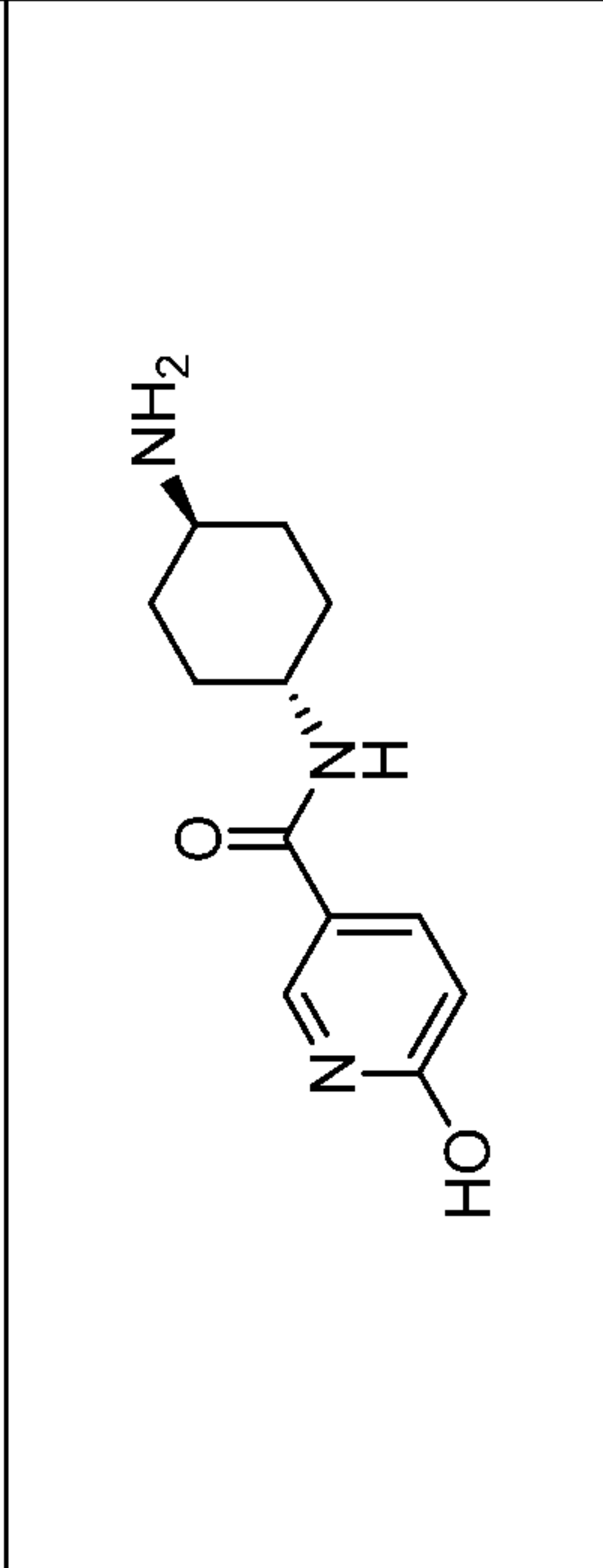
N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide;

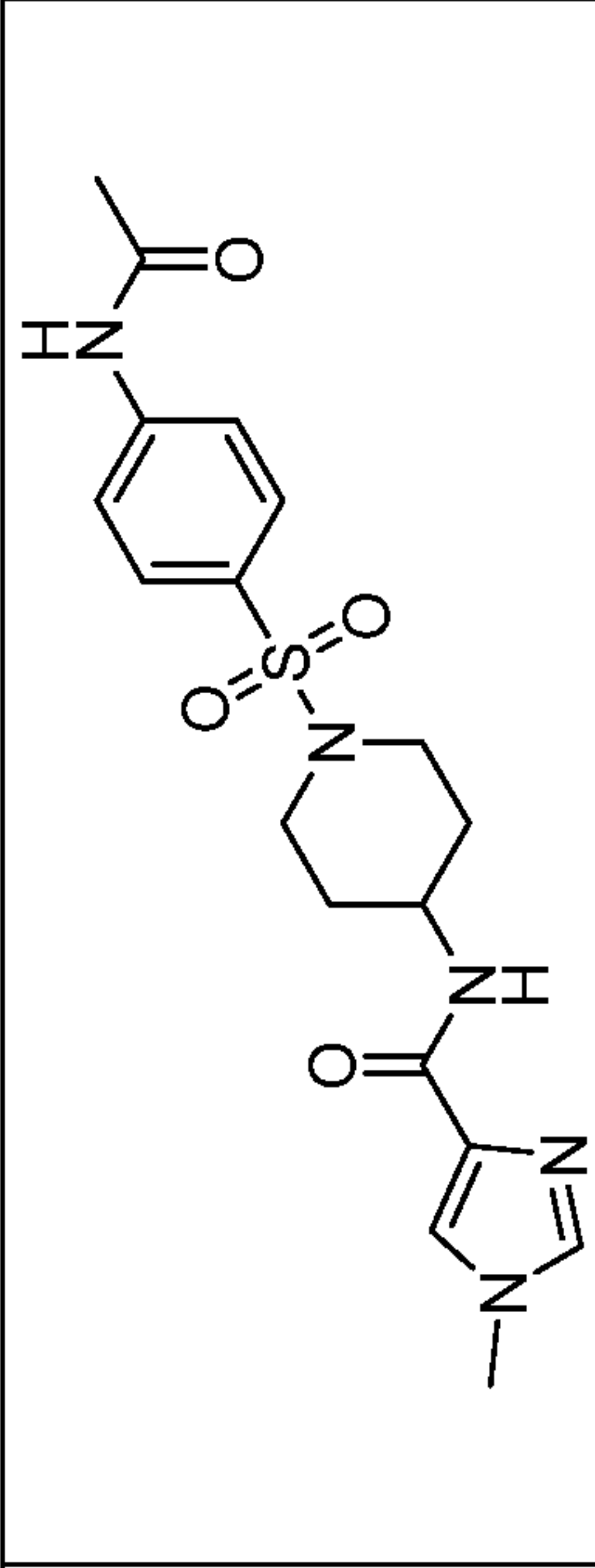
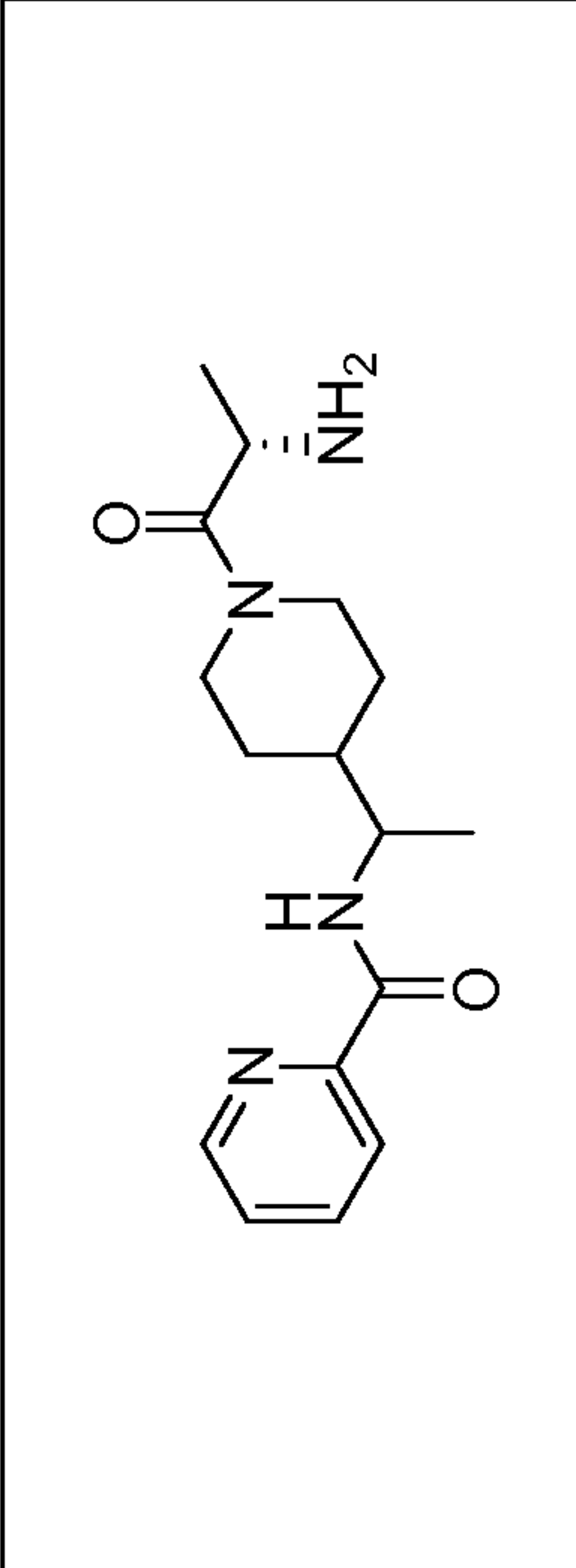
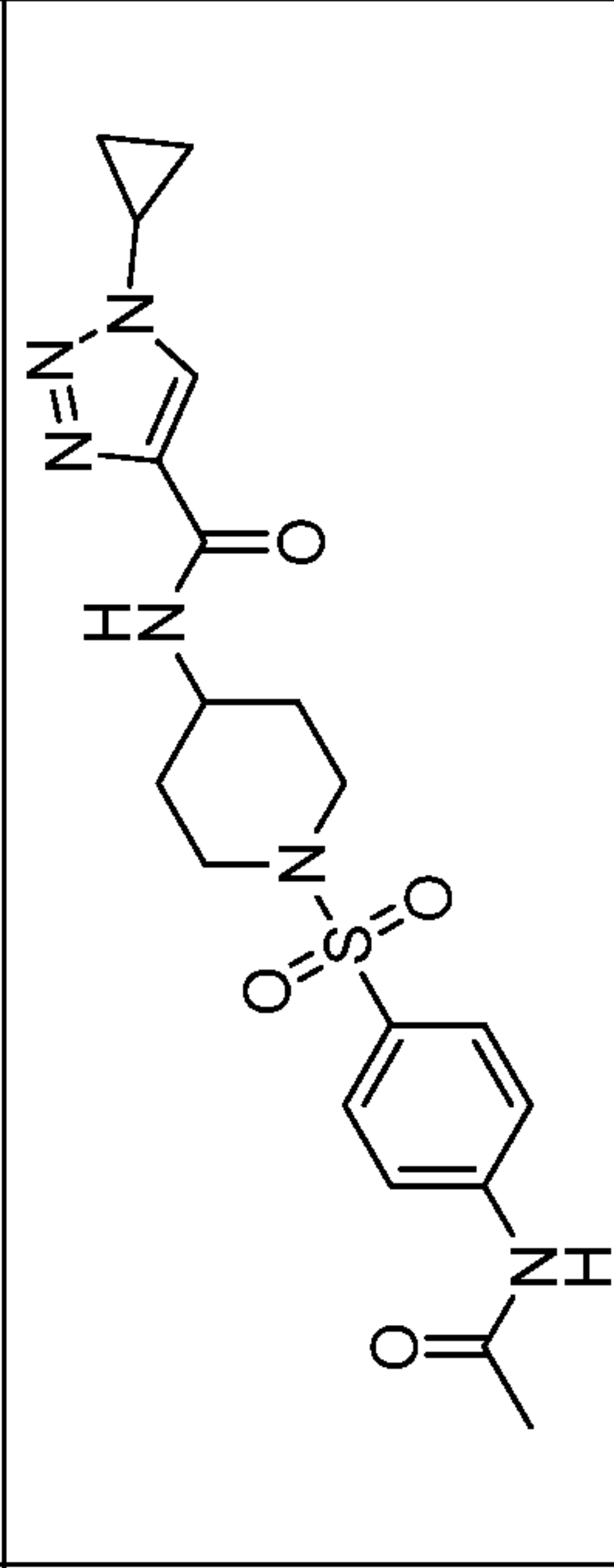
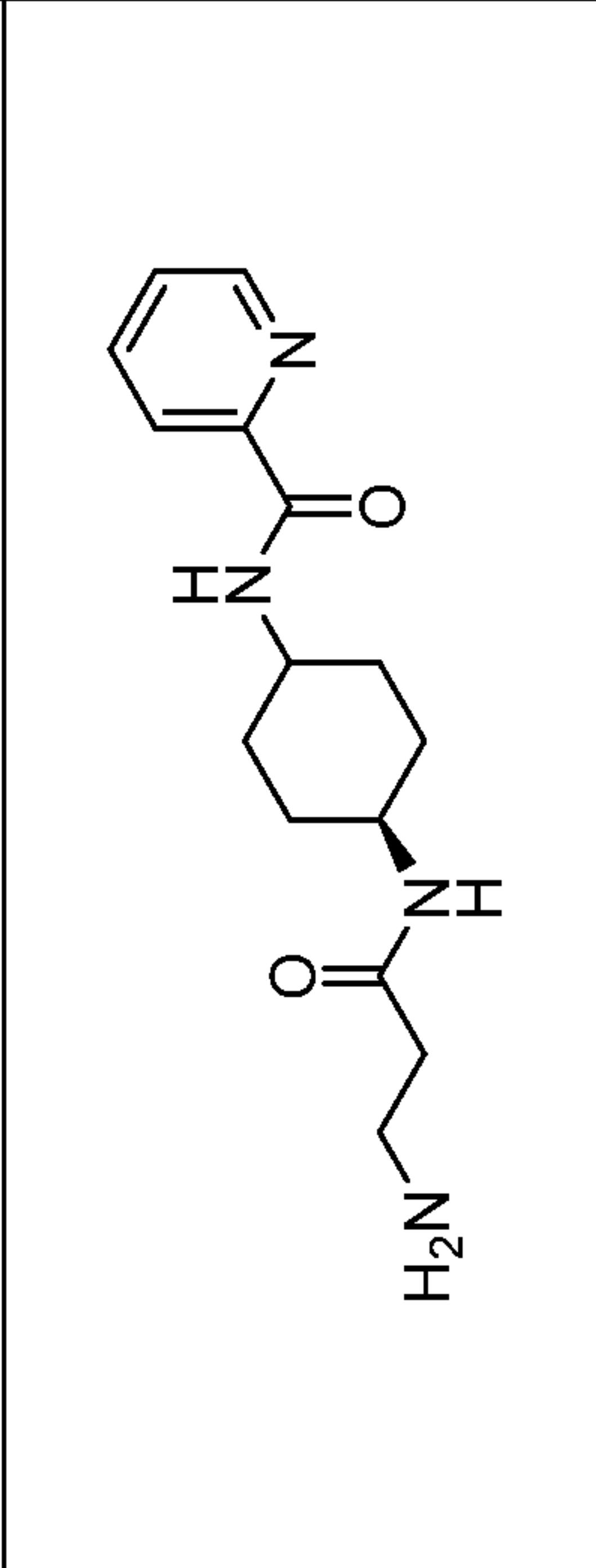
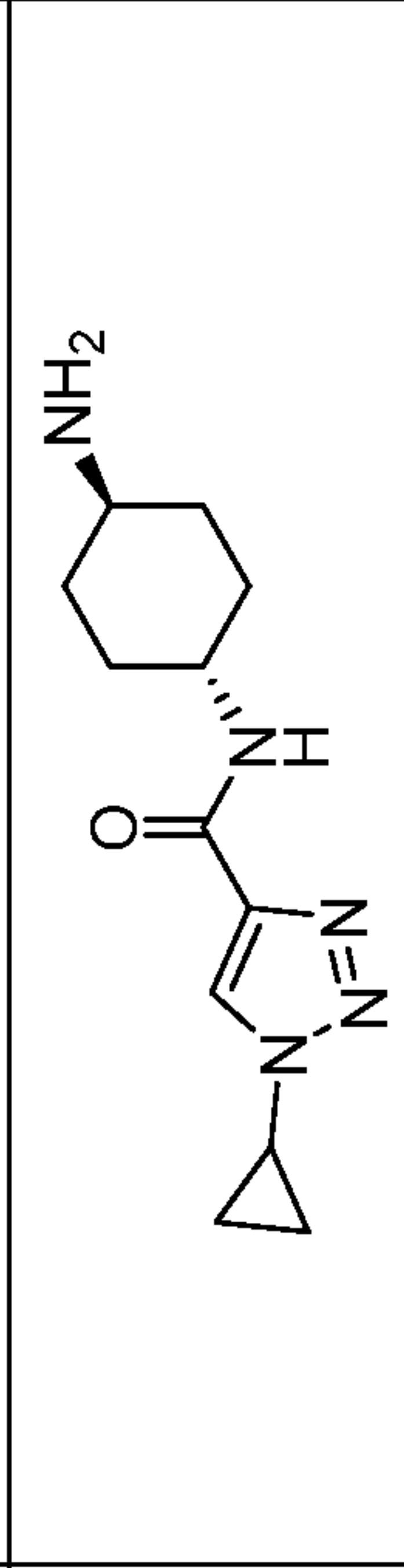
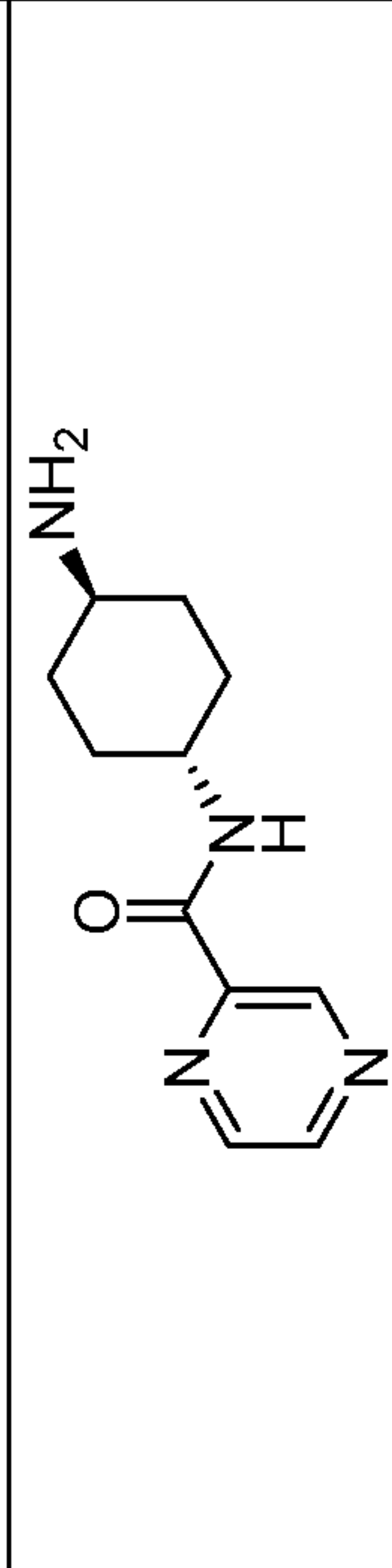
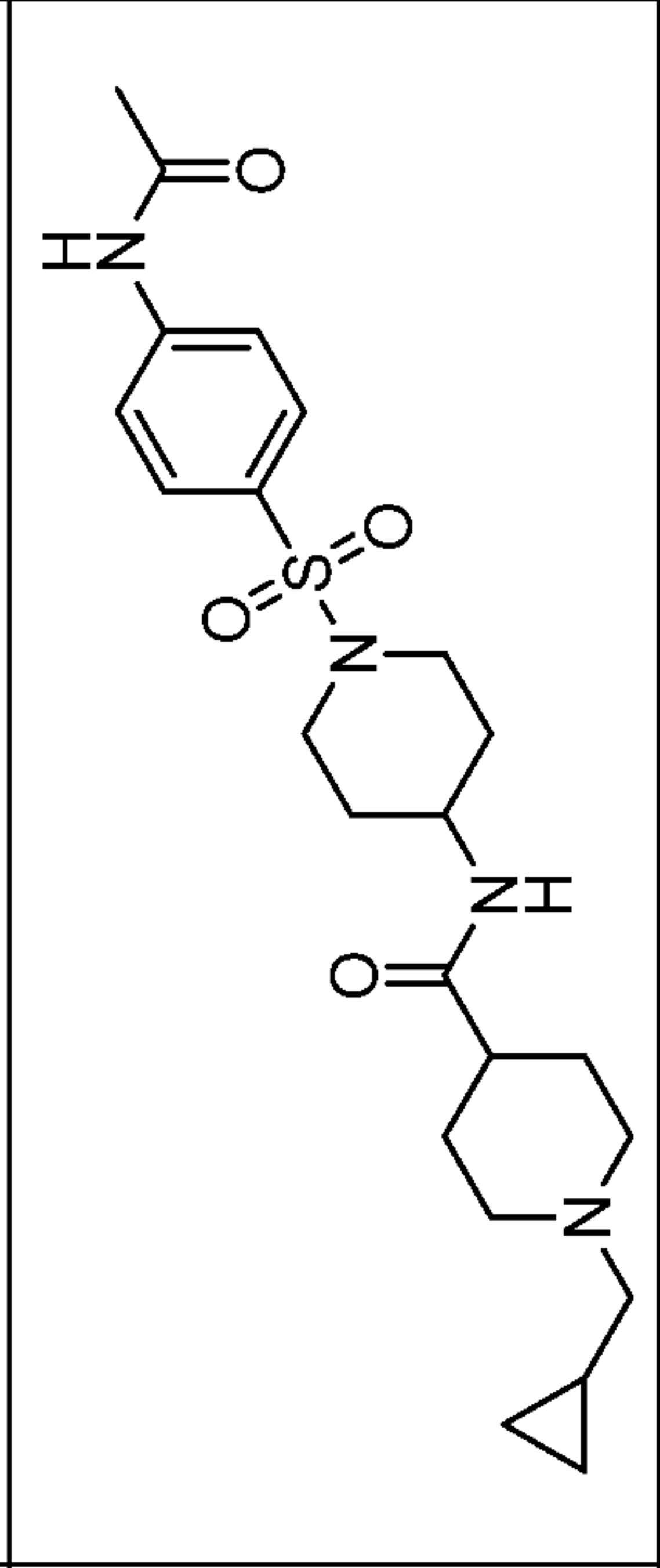
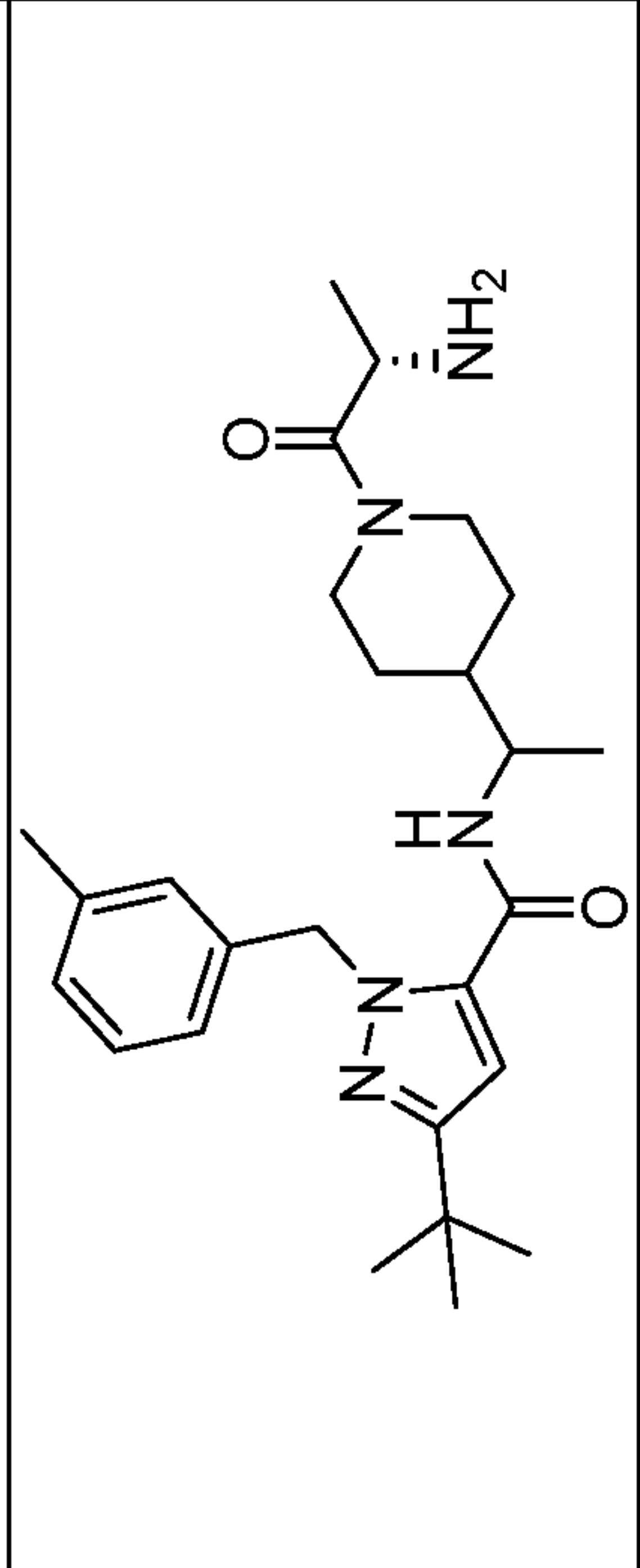
N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-4-cyclopropyl-1H-imidazole-2-carboxamide; and

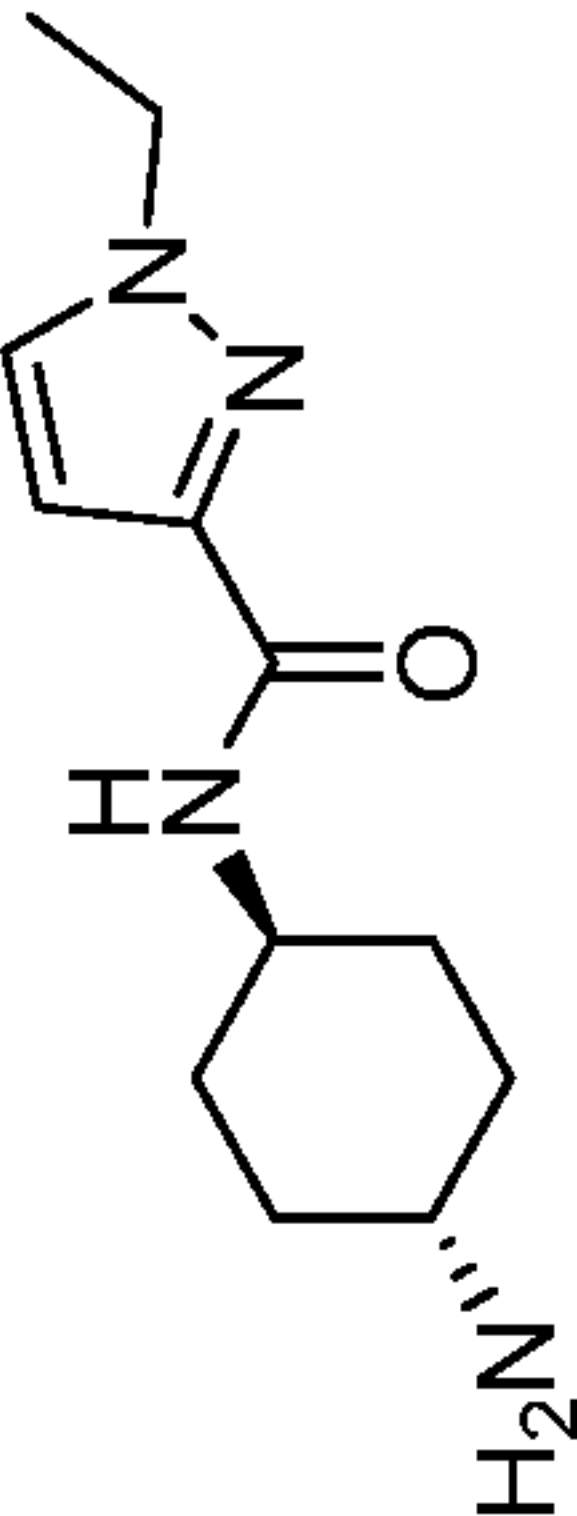
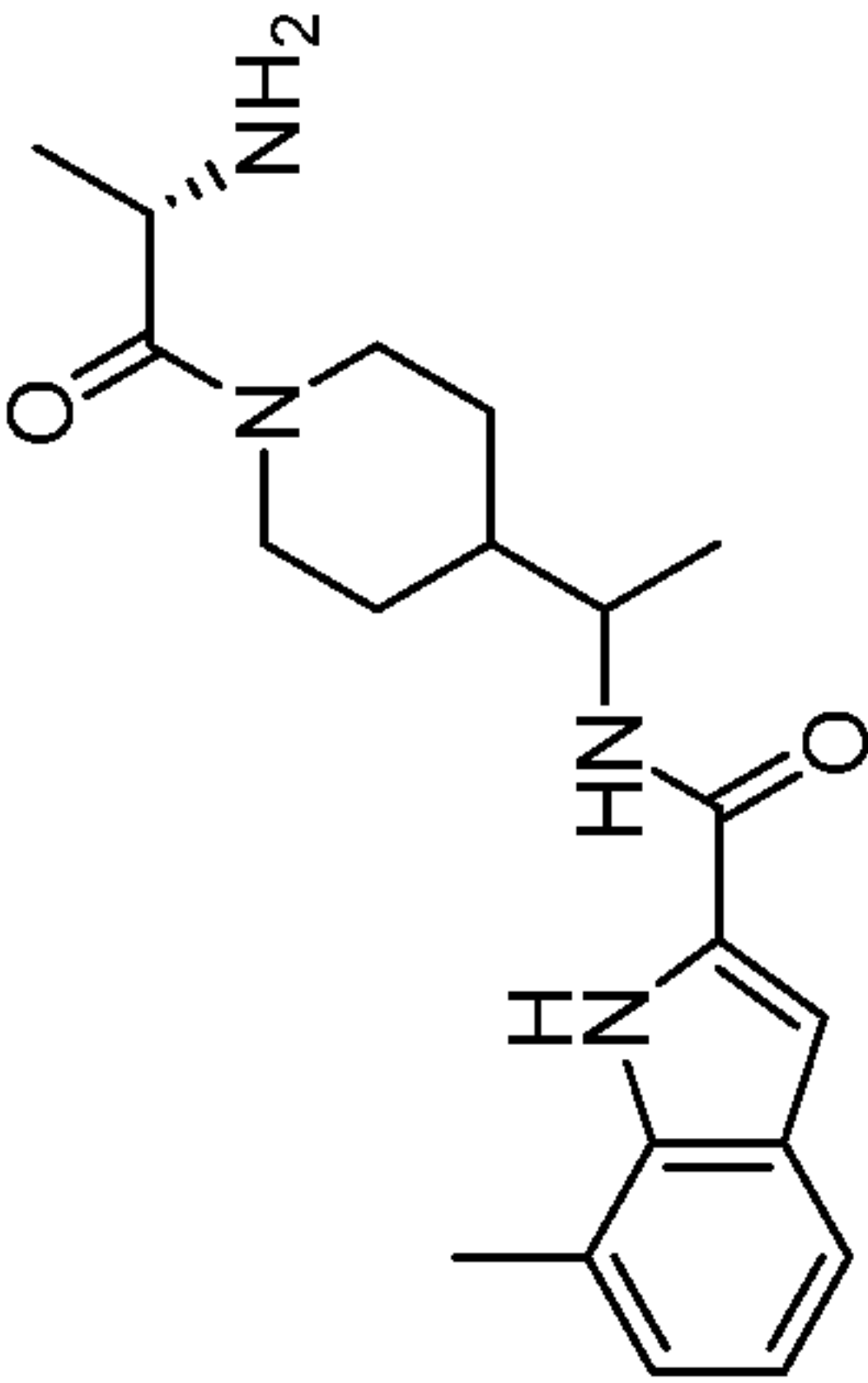
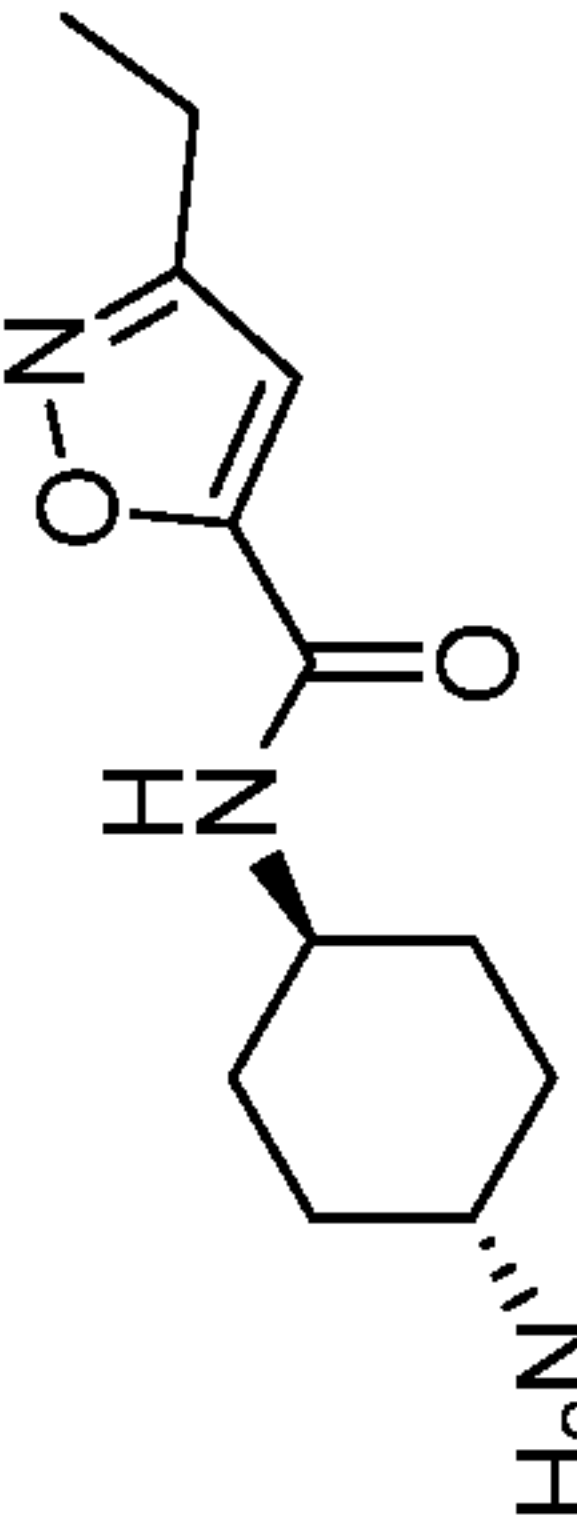
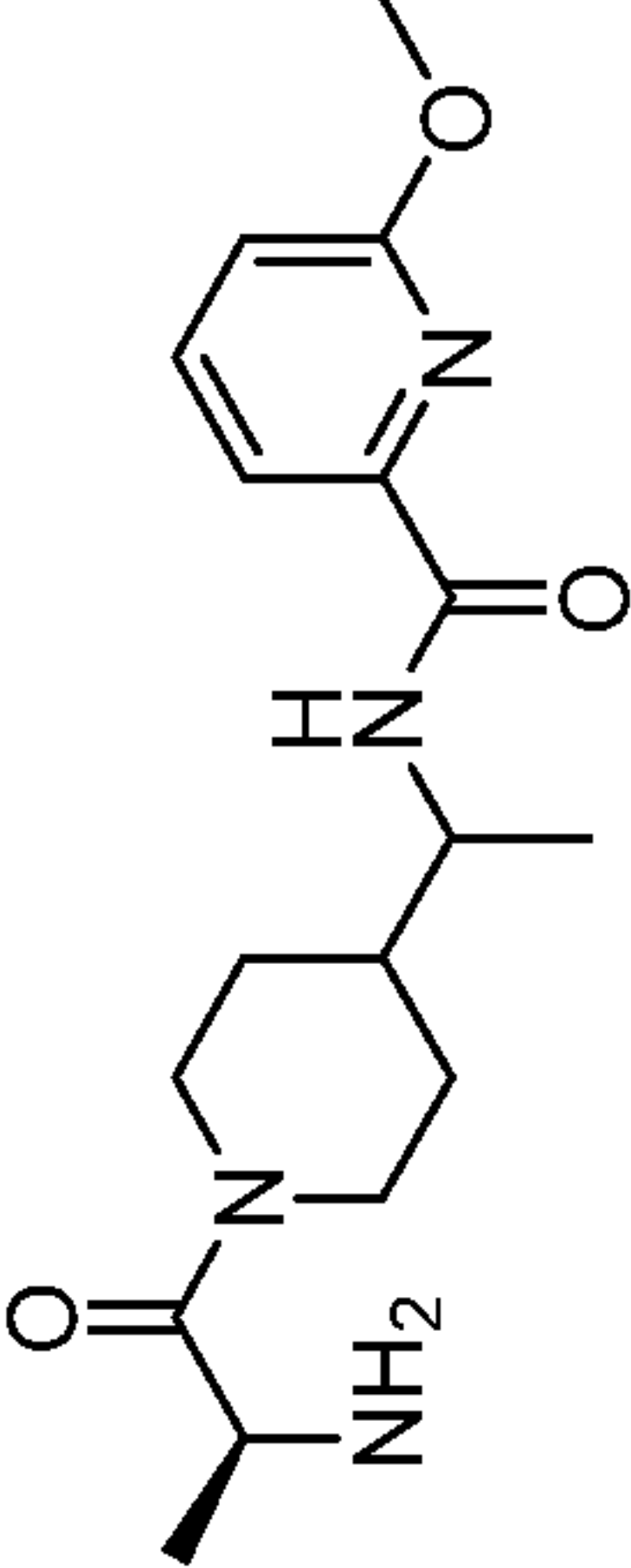
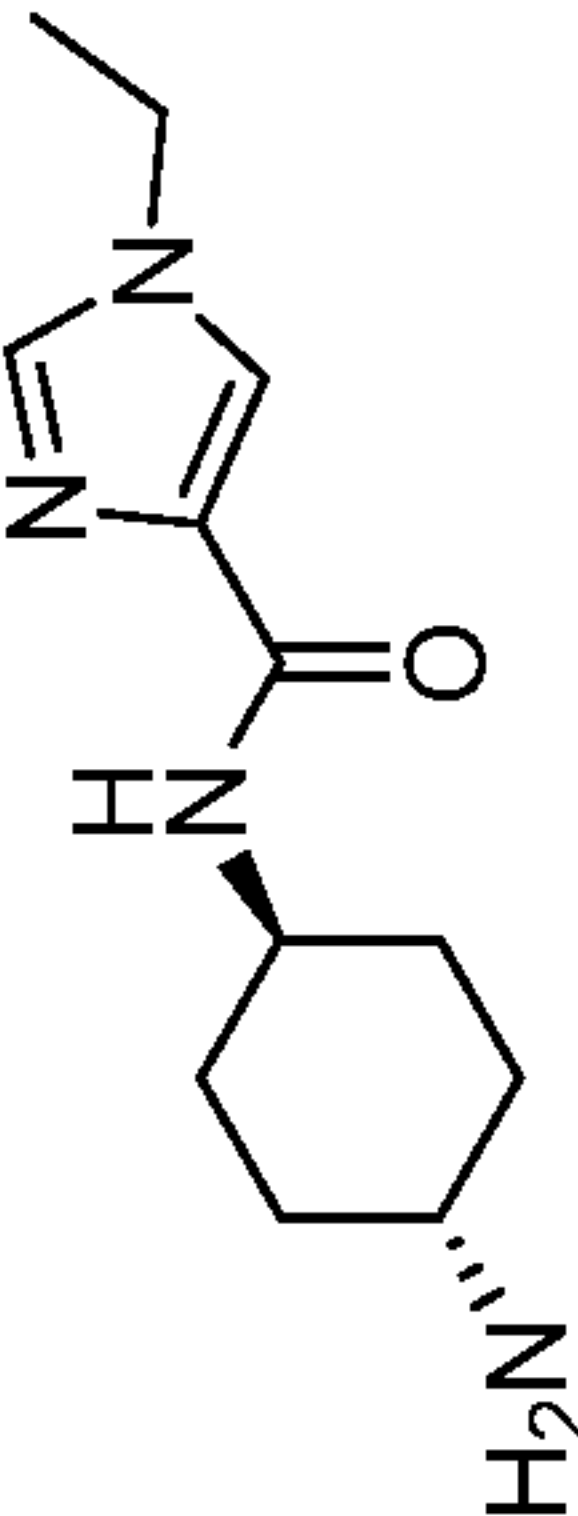
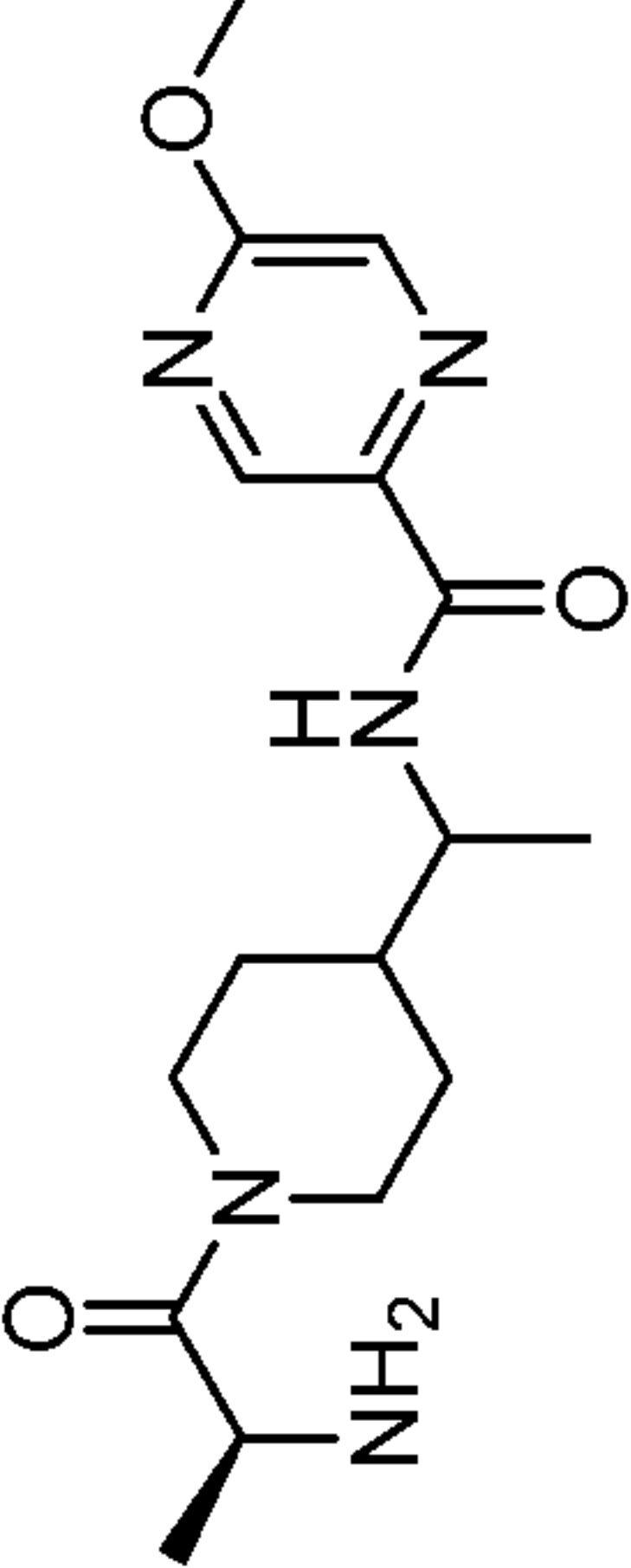
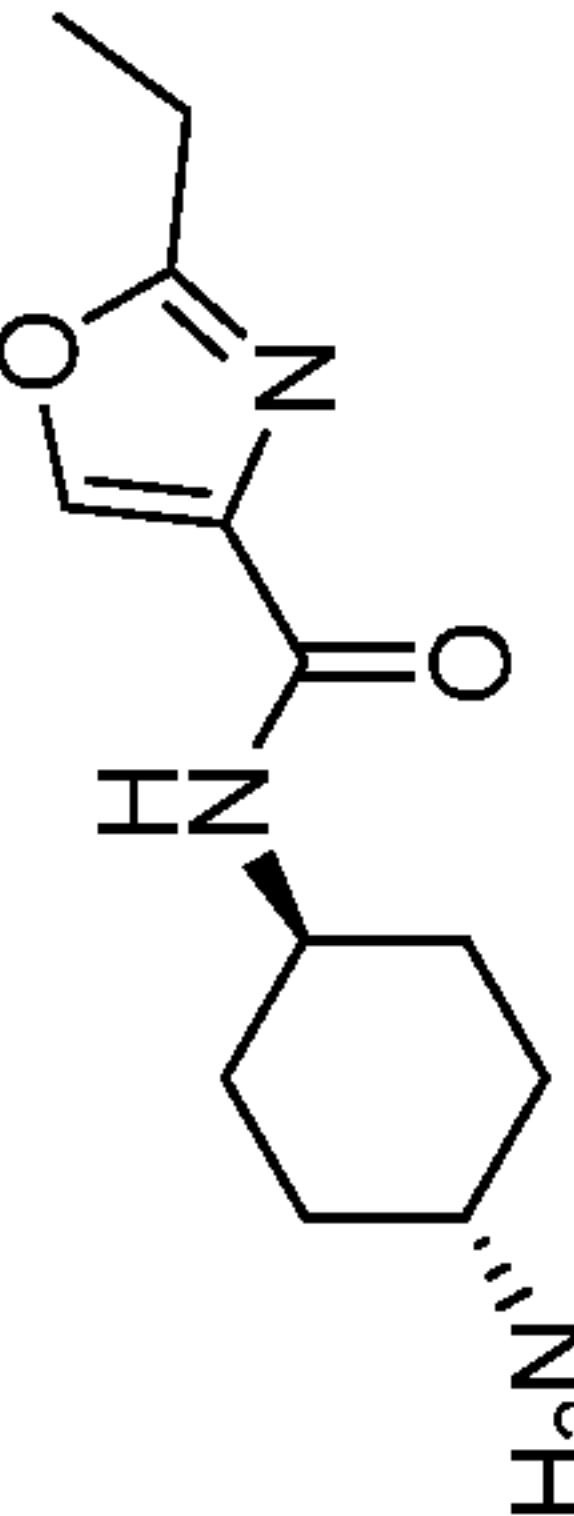
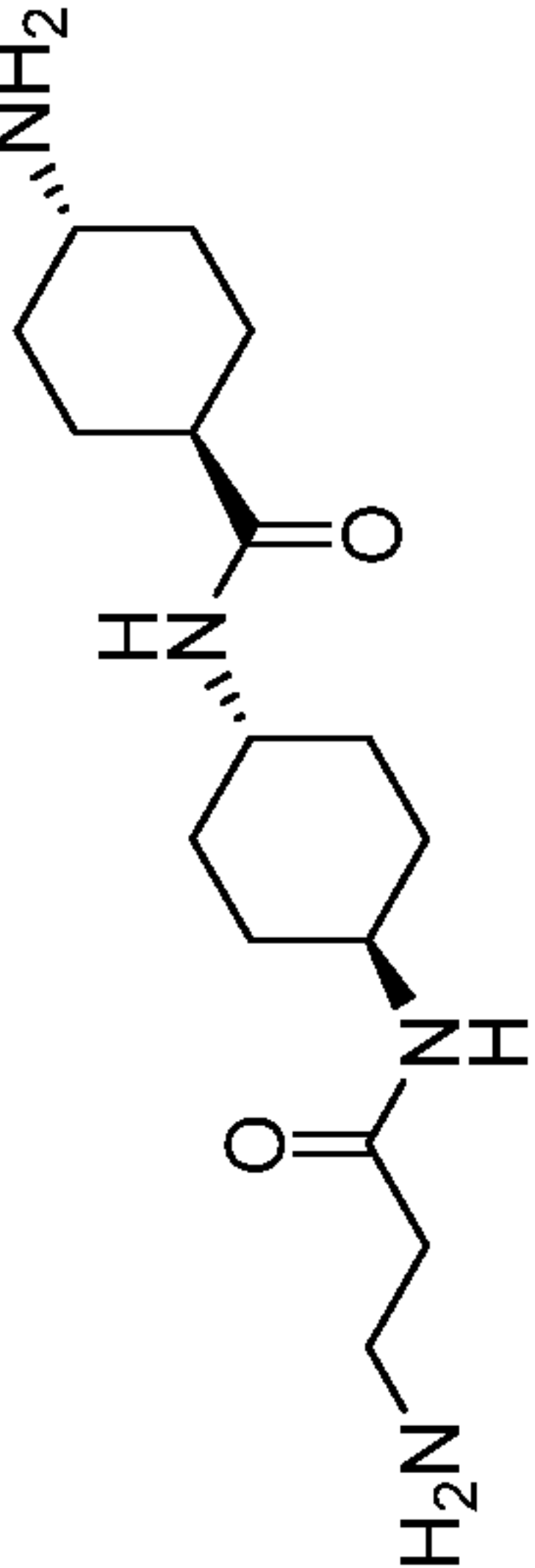
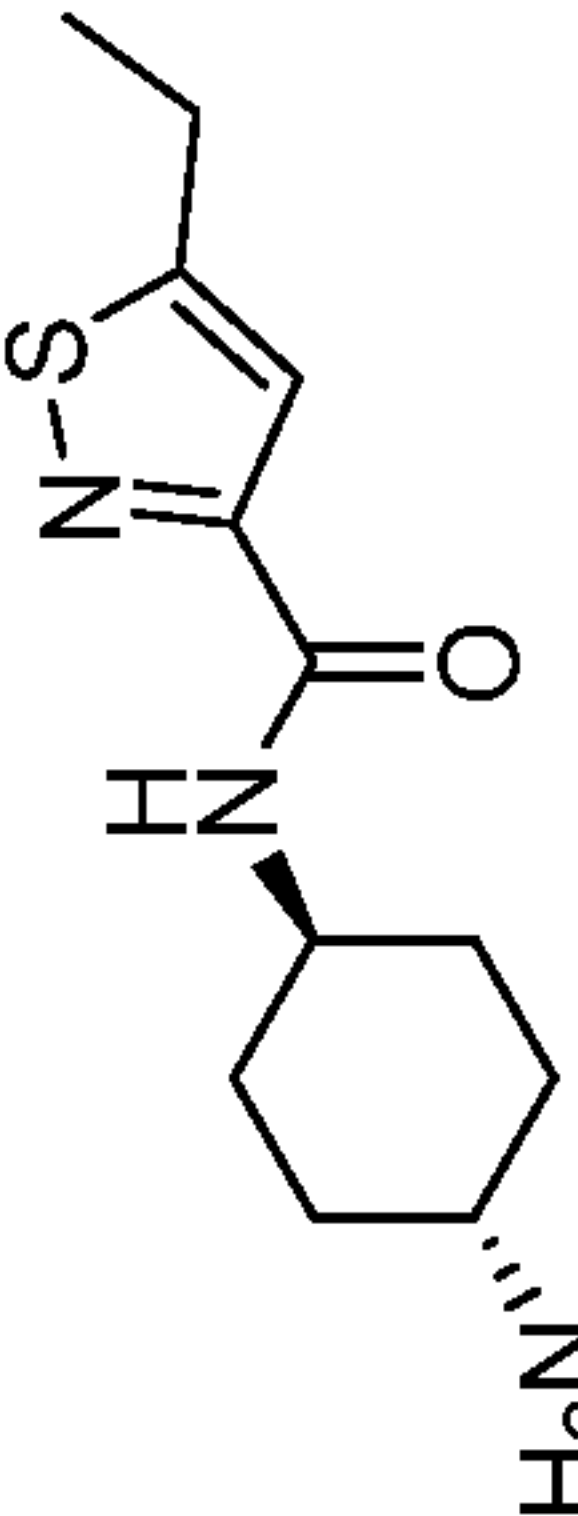
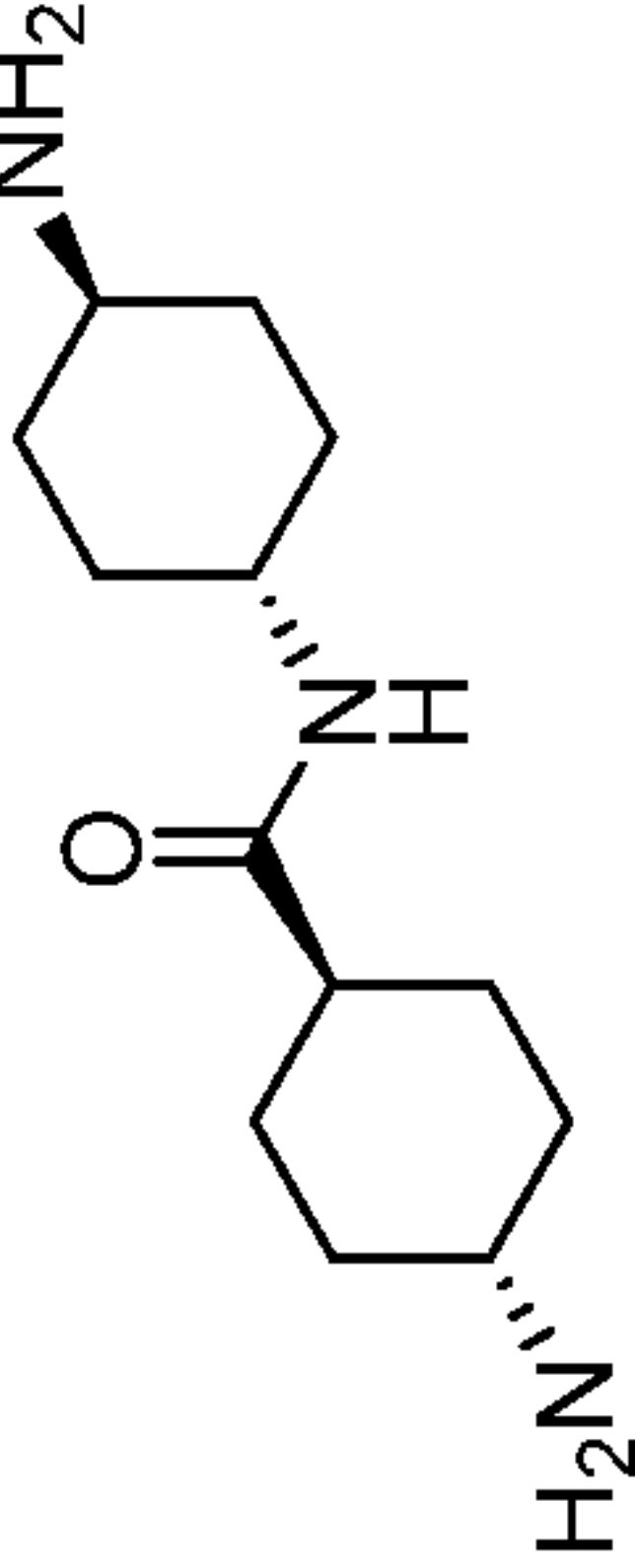
1-cyclopropyl-N-(1-((1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide,

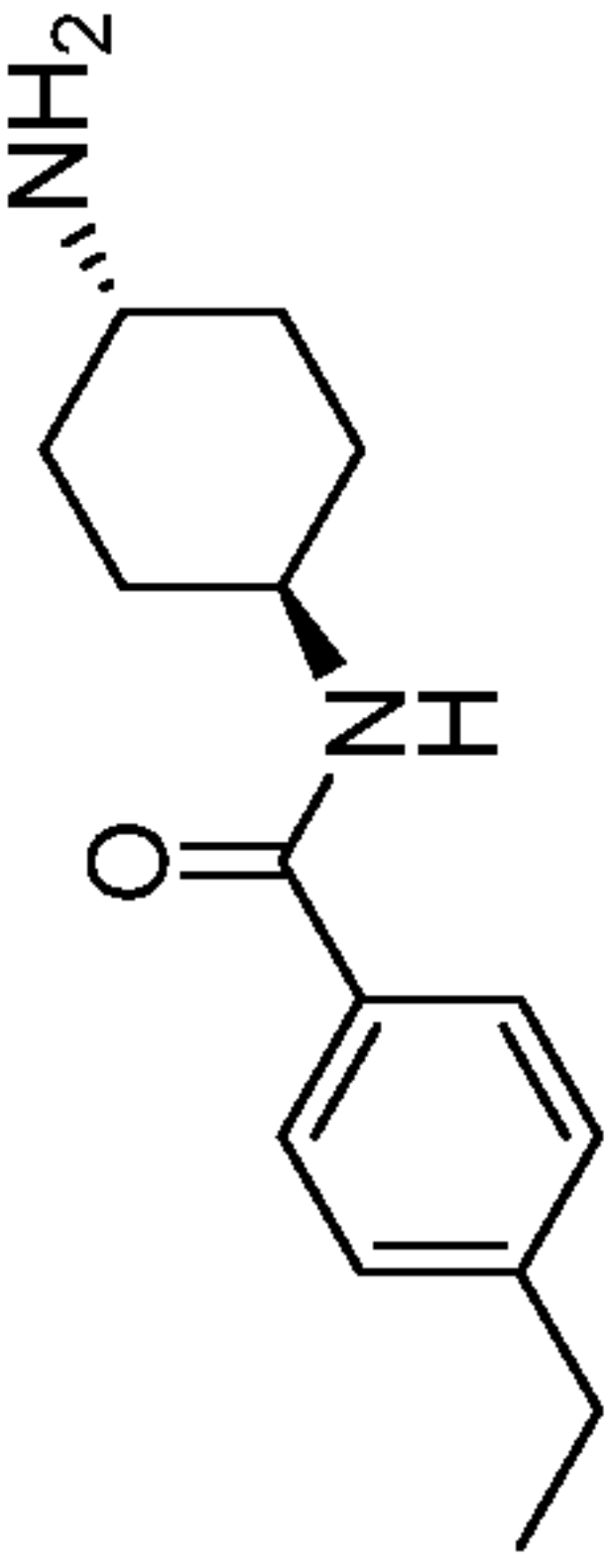
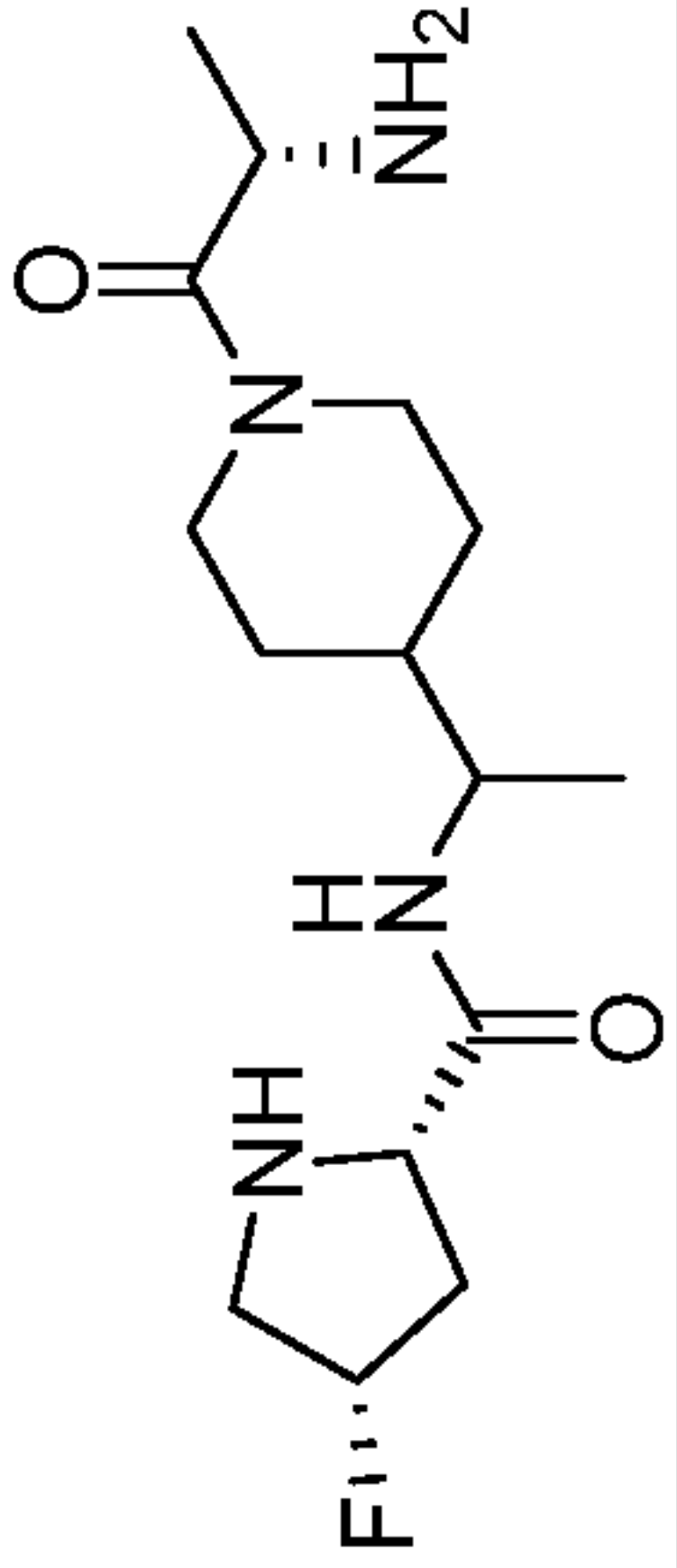
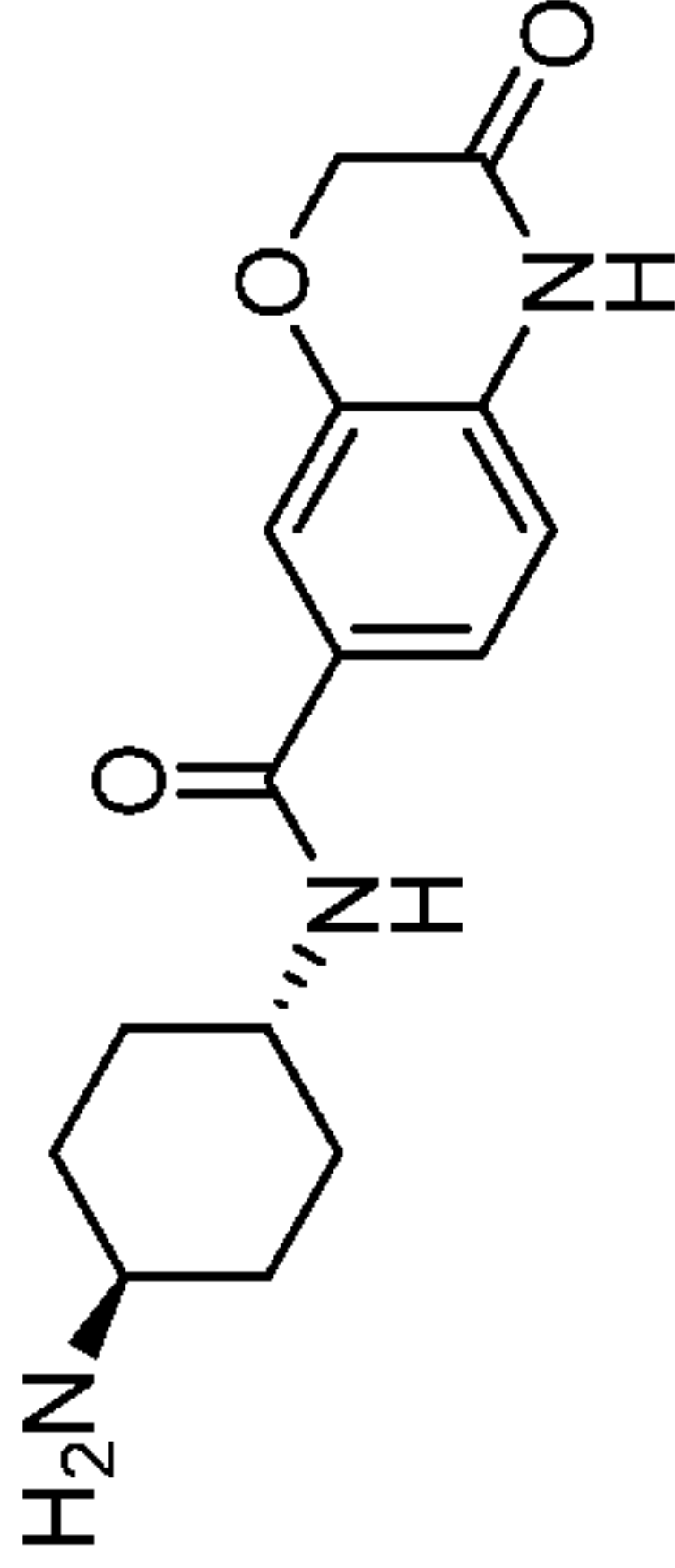
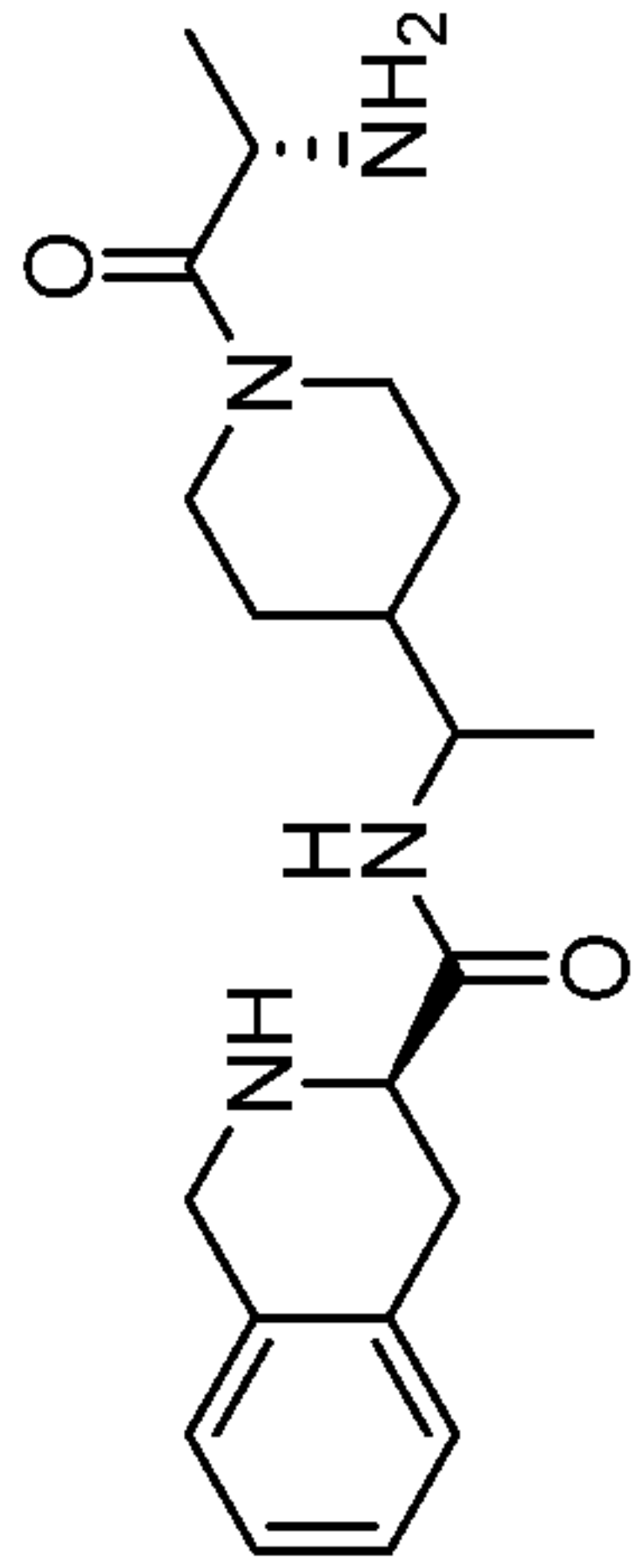
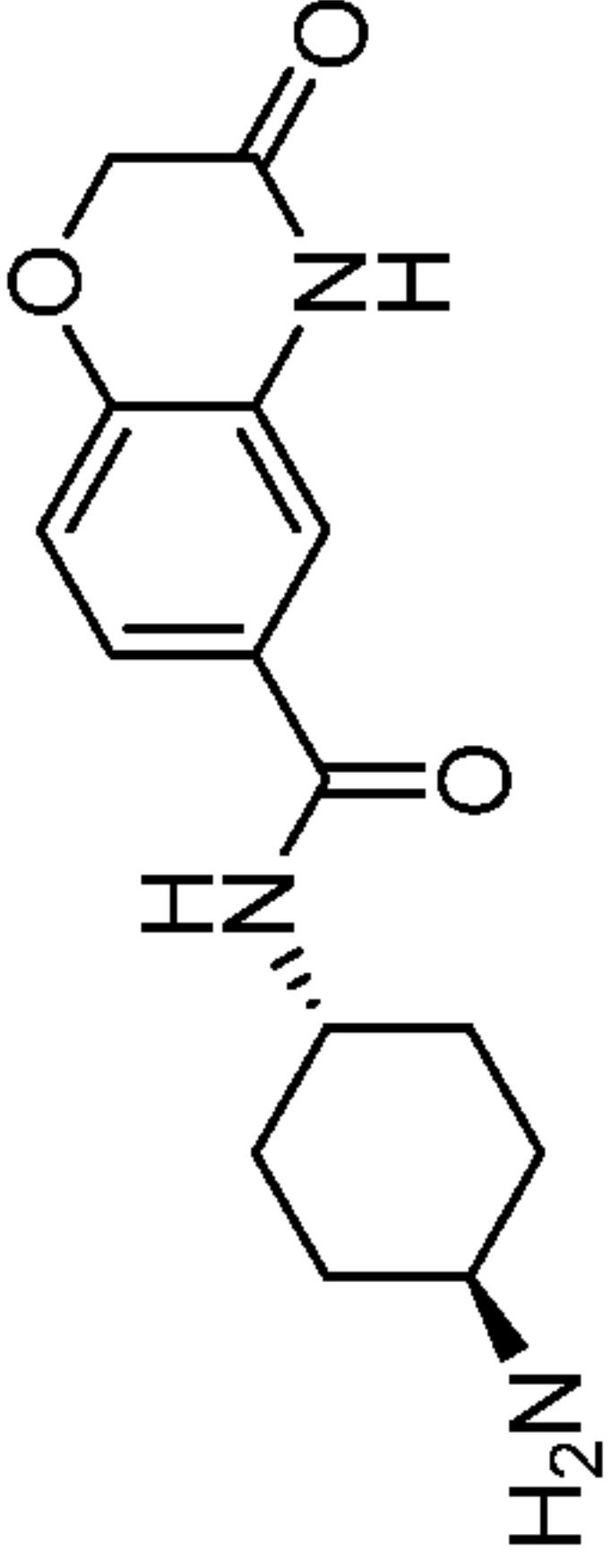
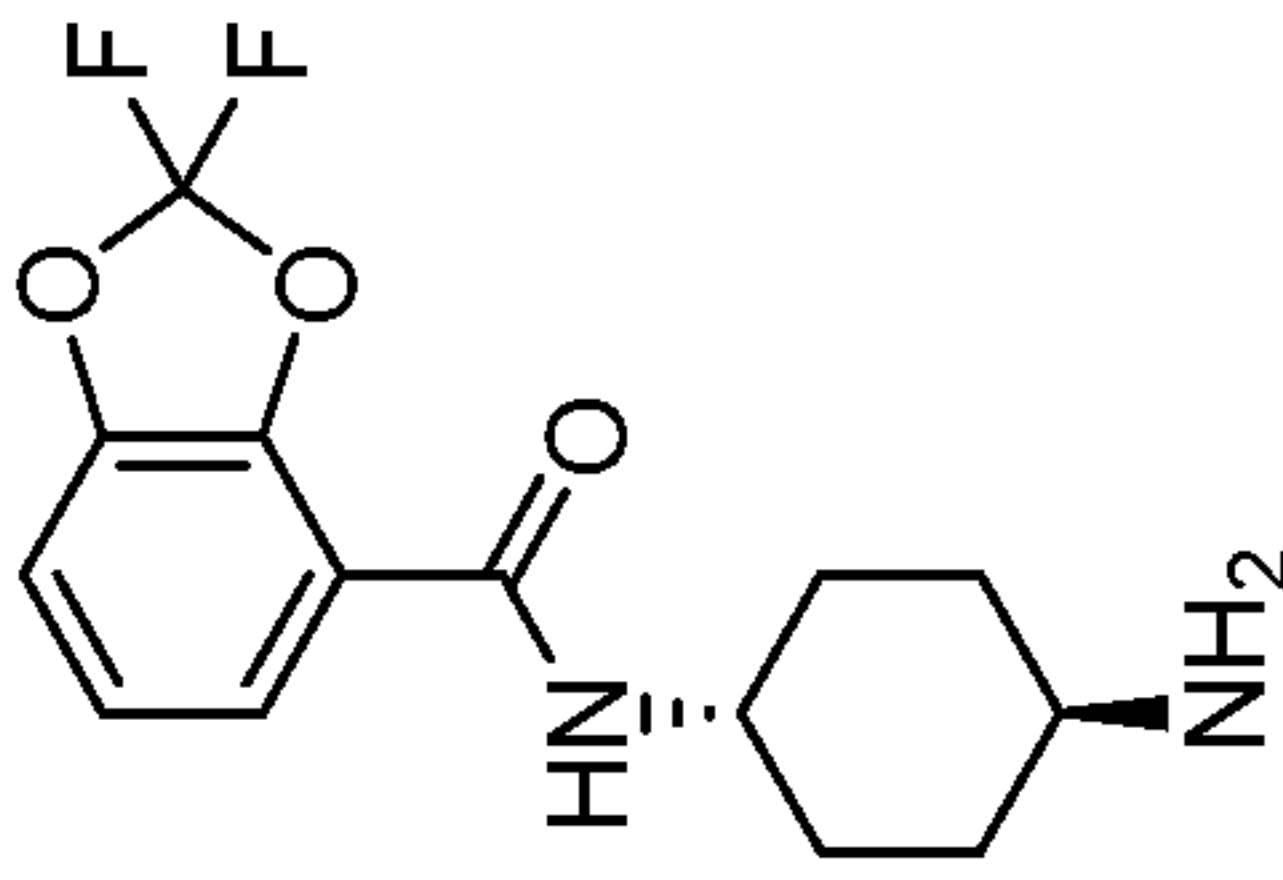
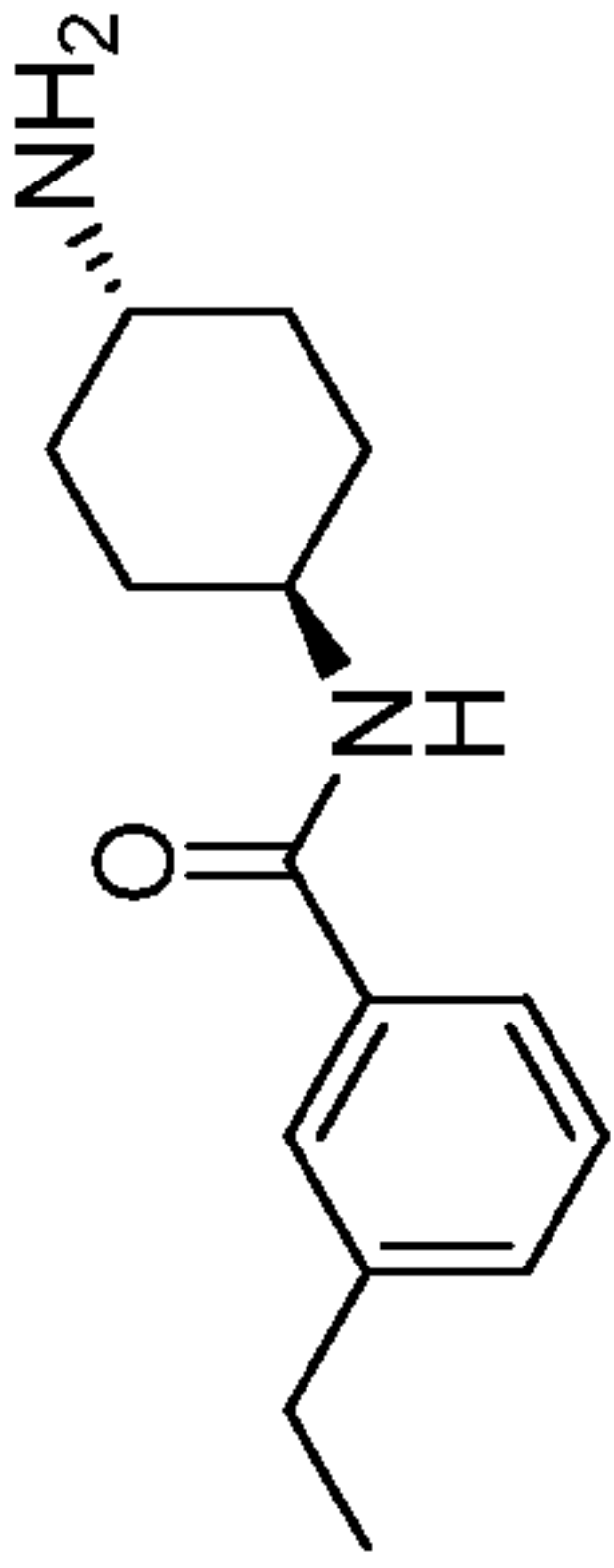
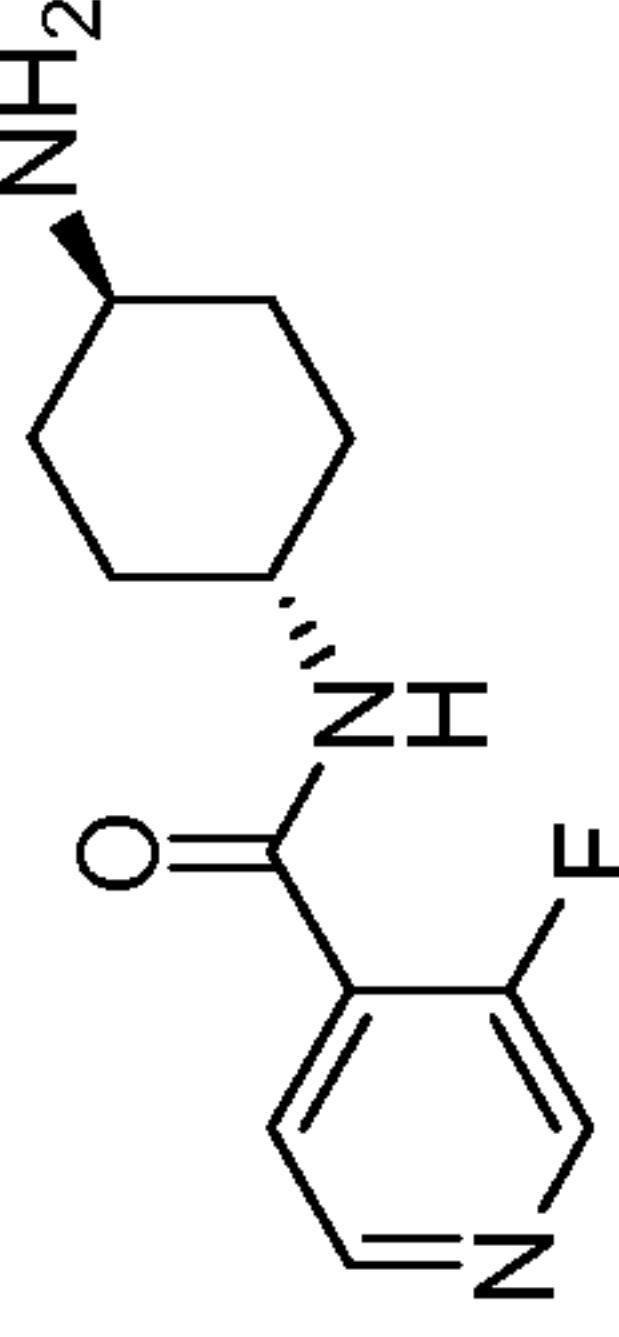
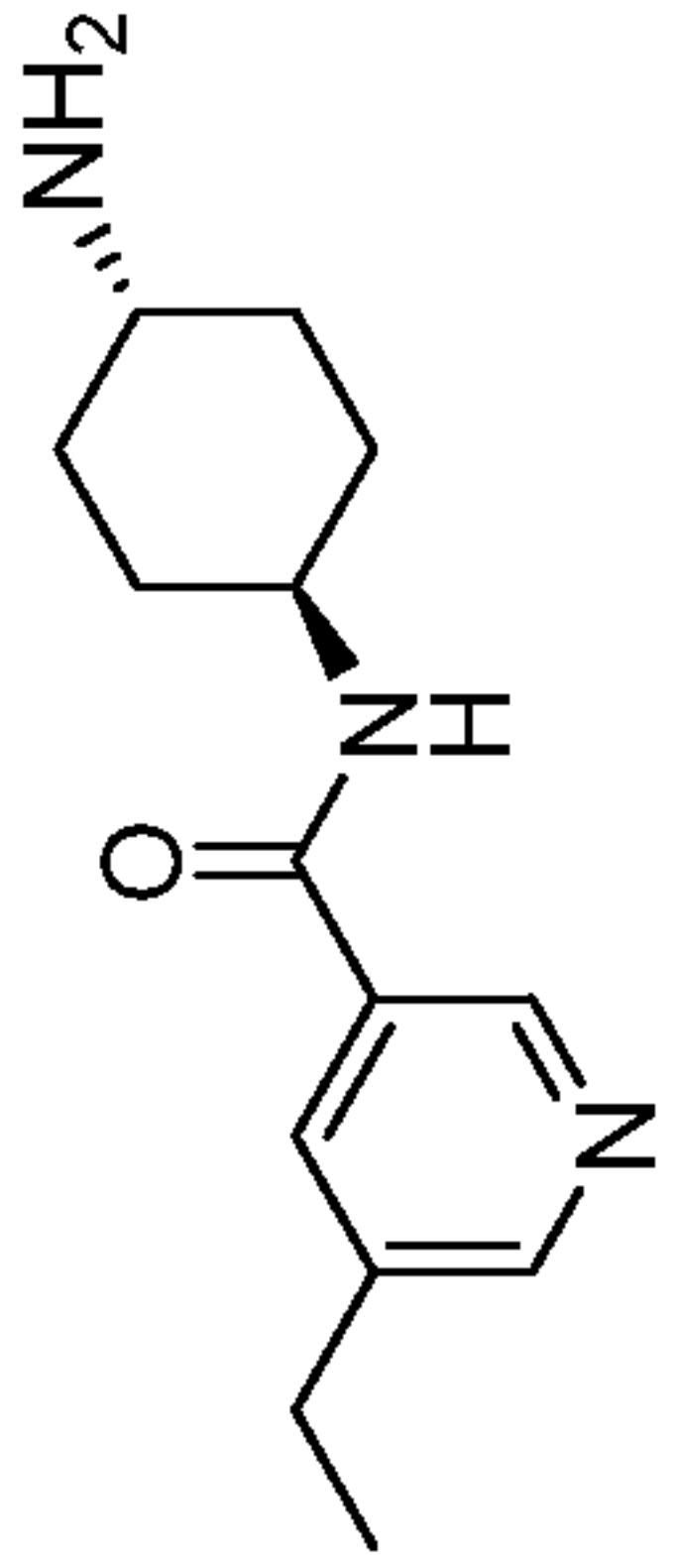
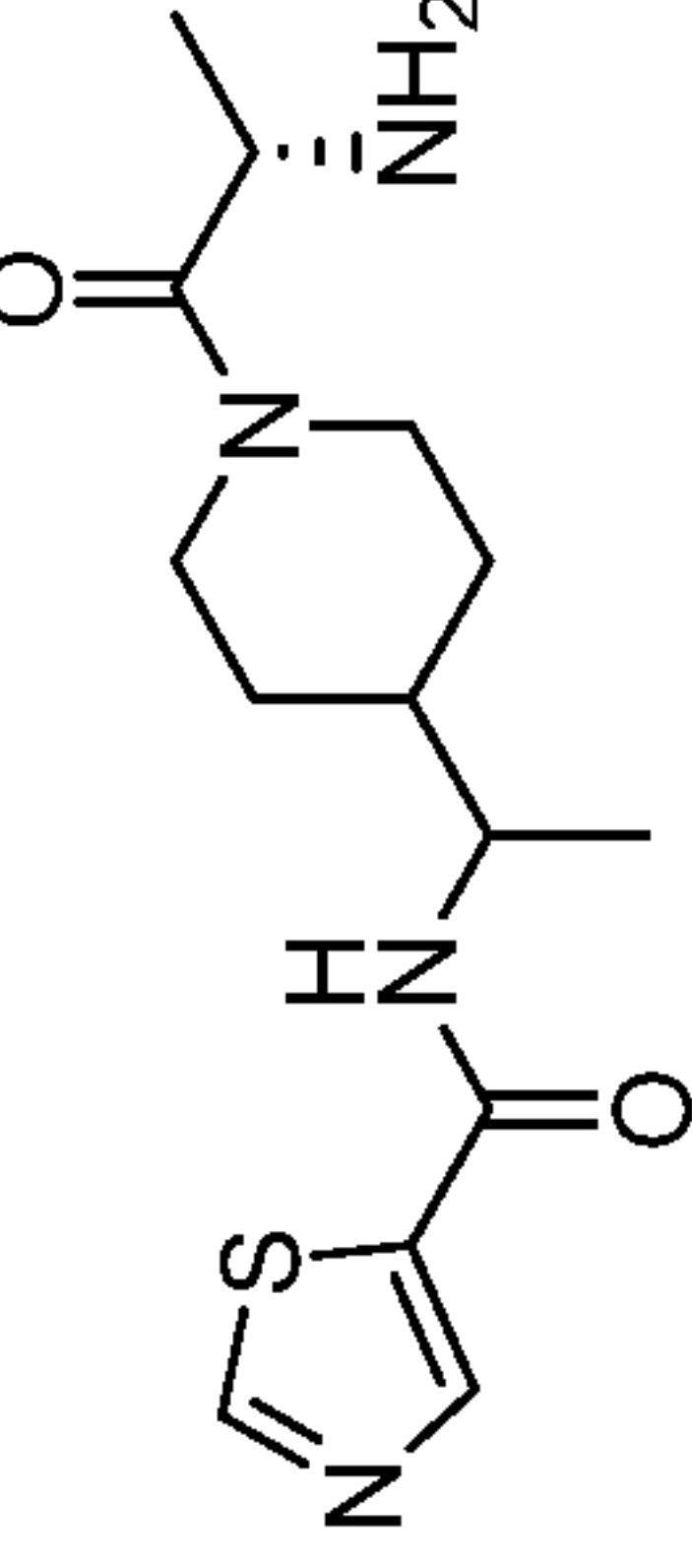
and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof.

[0103] It should be appreciated that the Compounds of the Disclosure in certain embodiments are the free base, various salts, and hydrate forms, and are not limited to the particular salt listed in Tables 1 and 3-6.

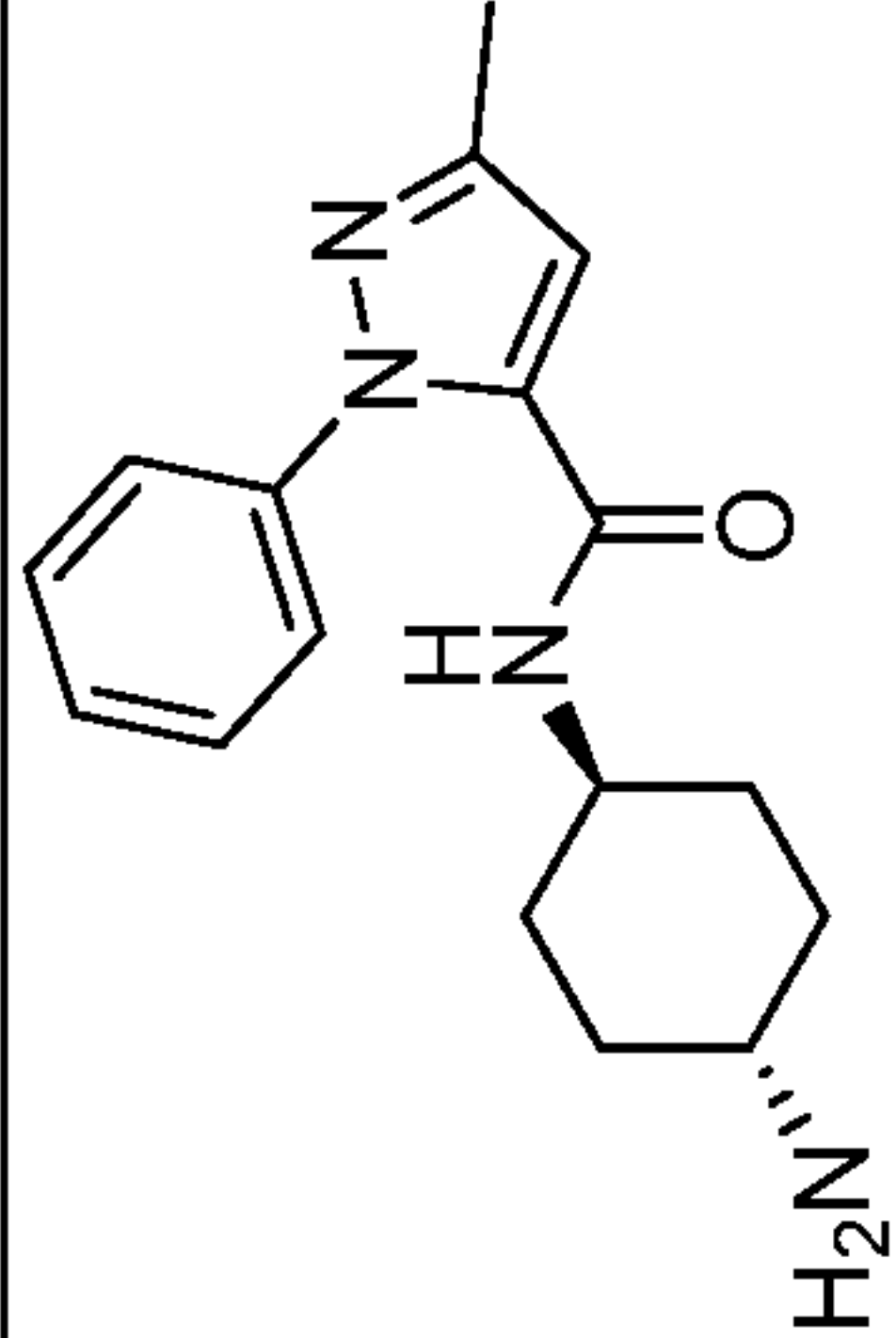
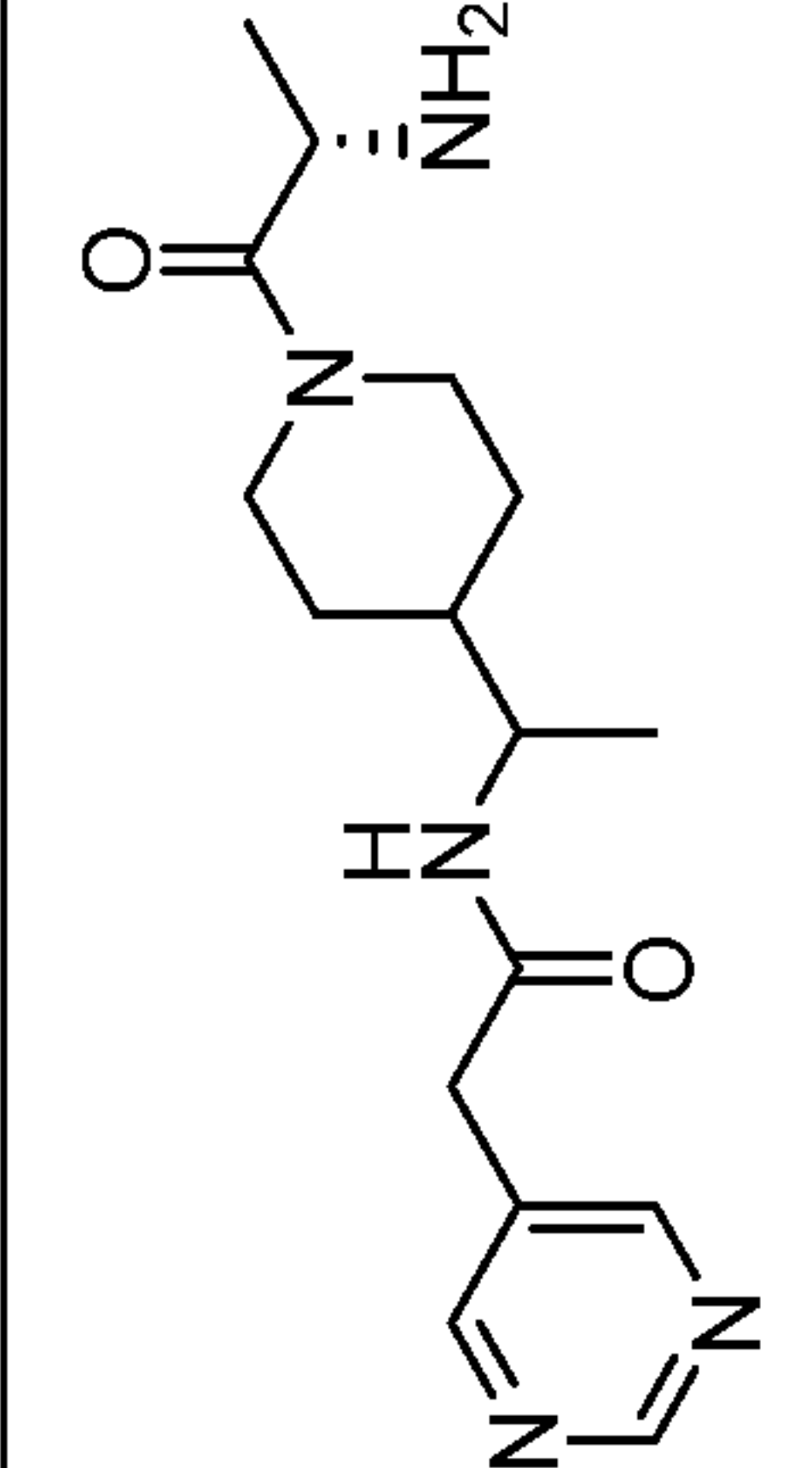
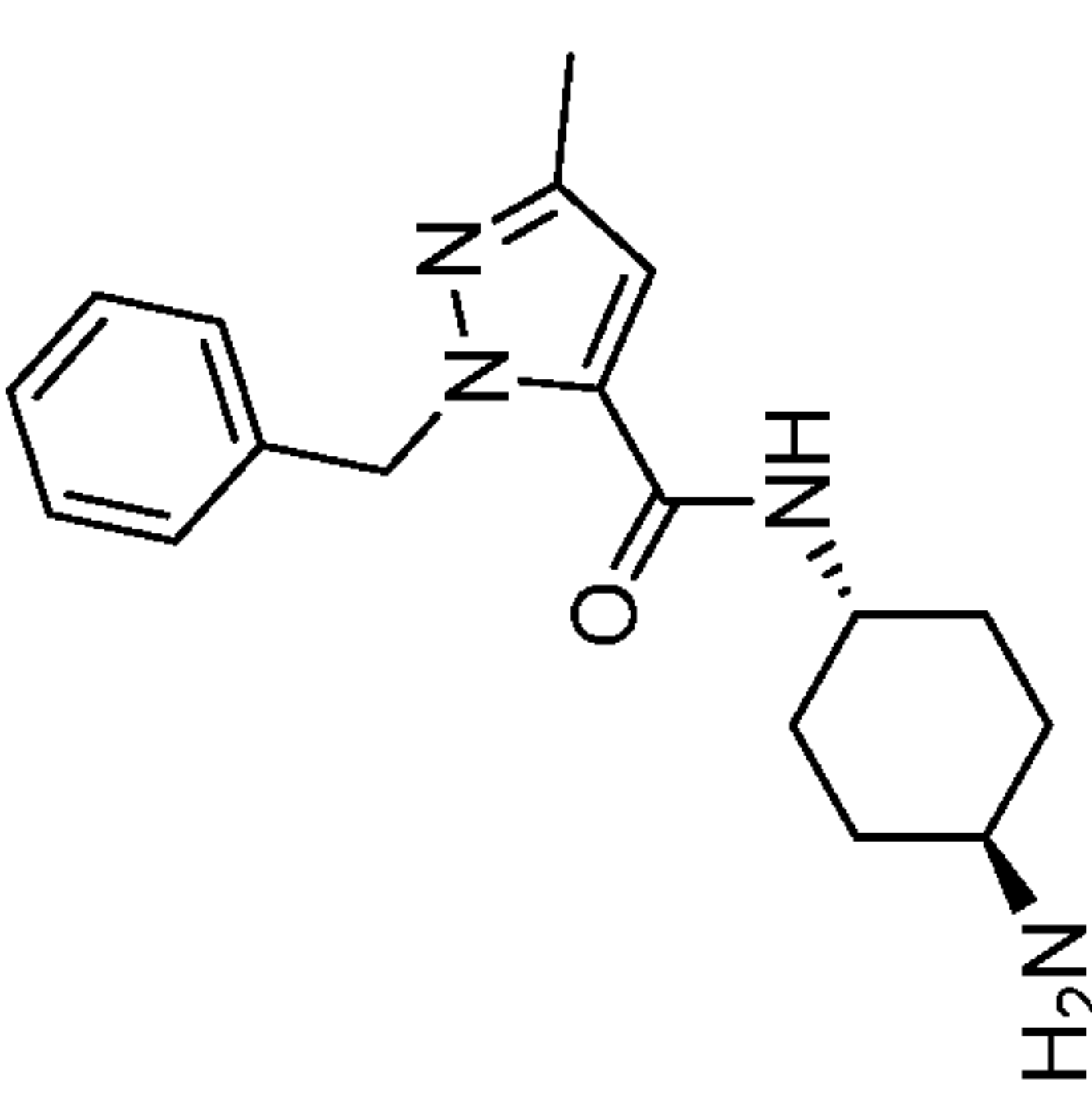
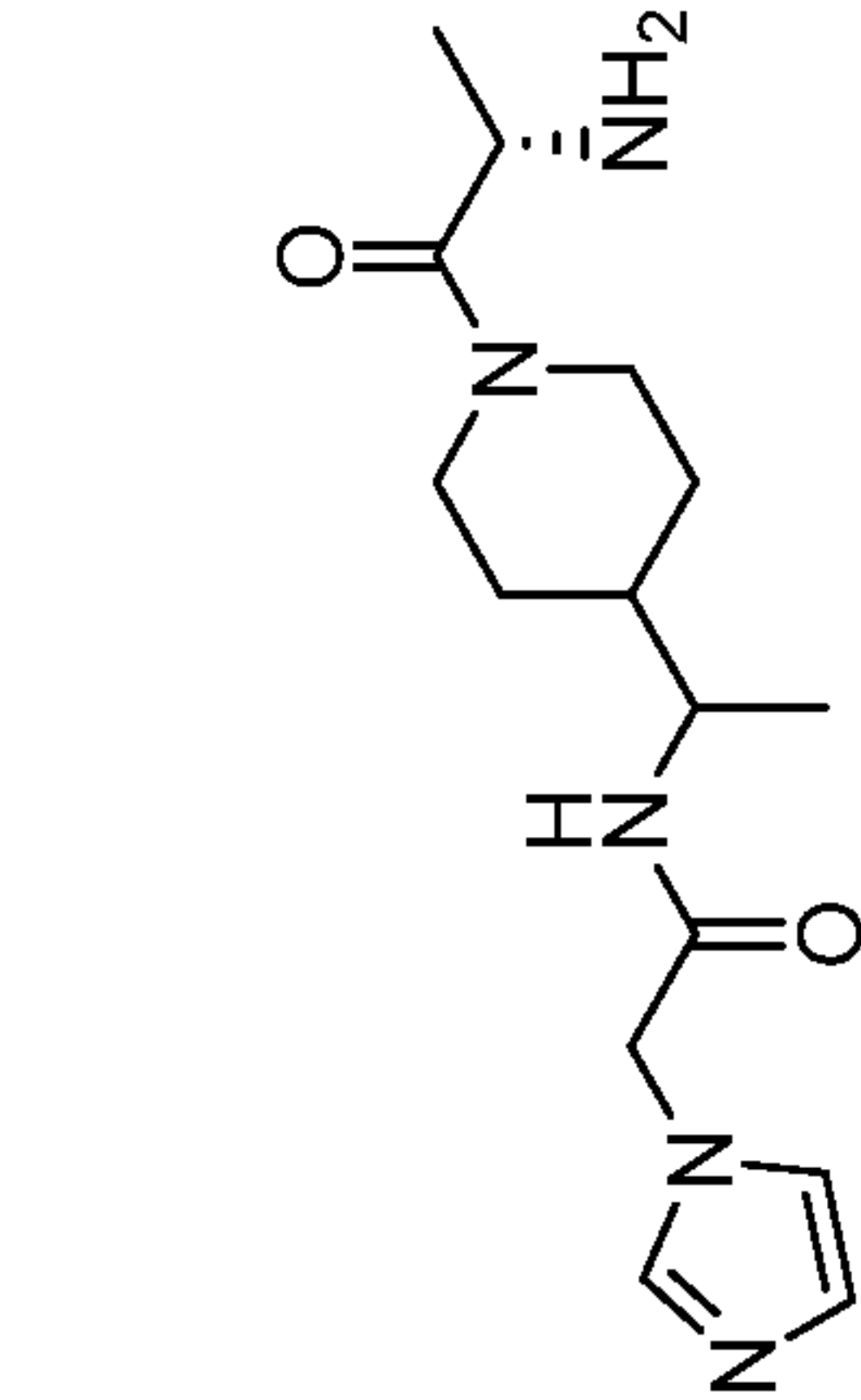
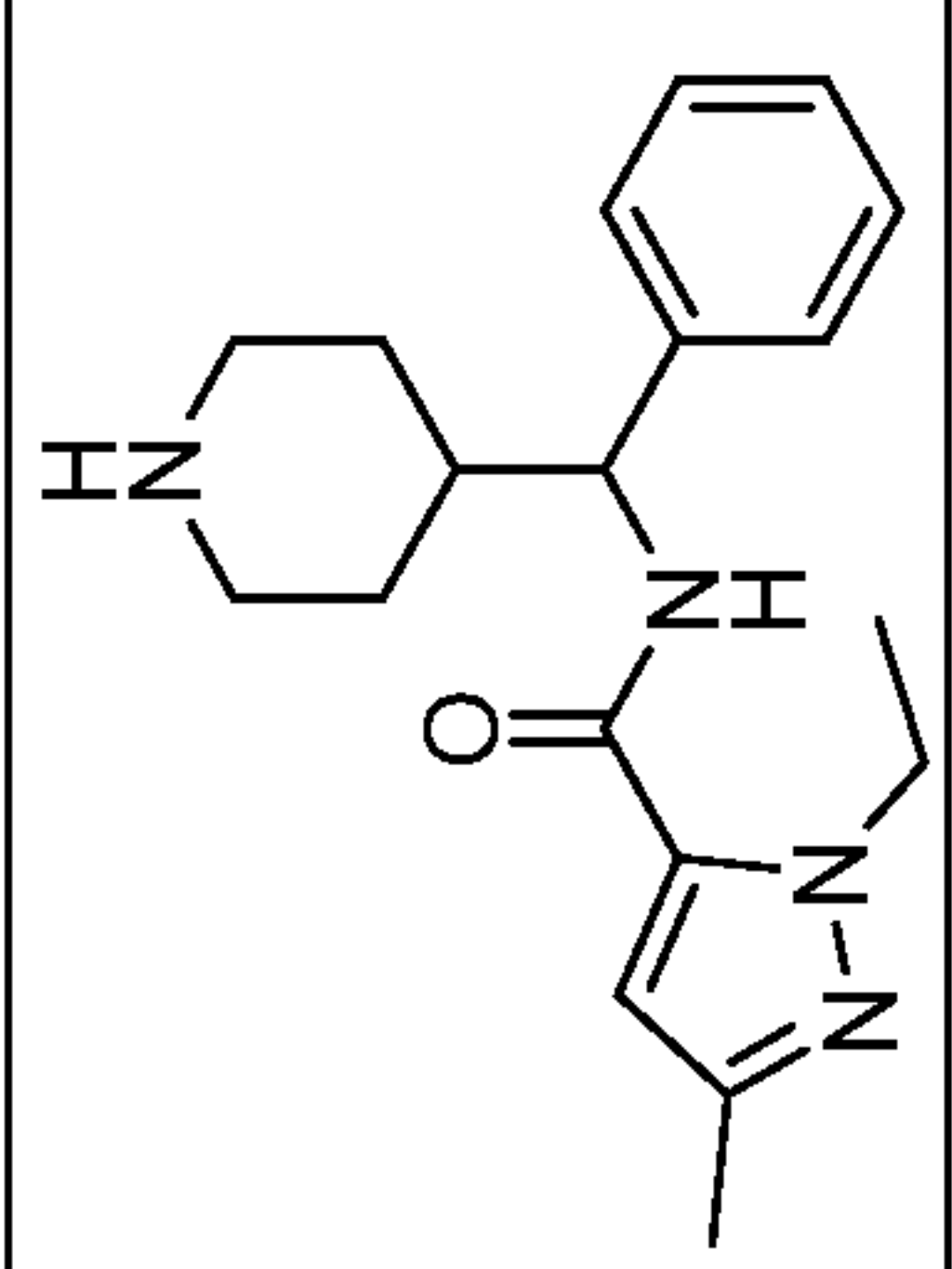
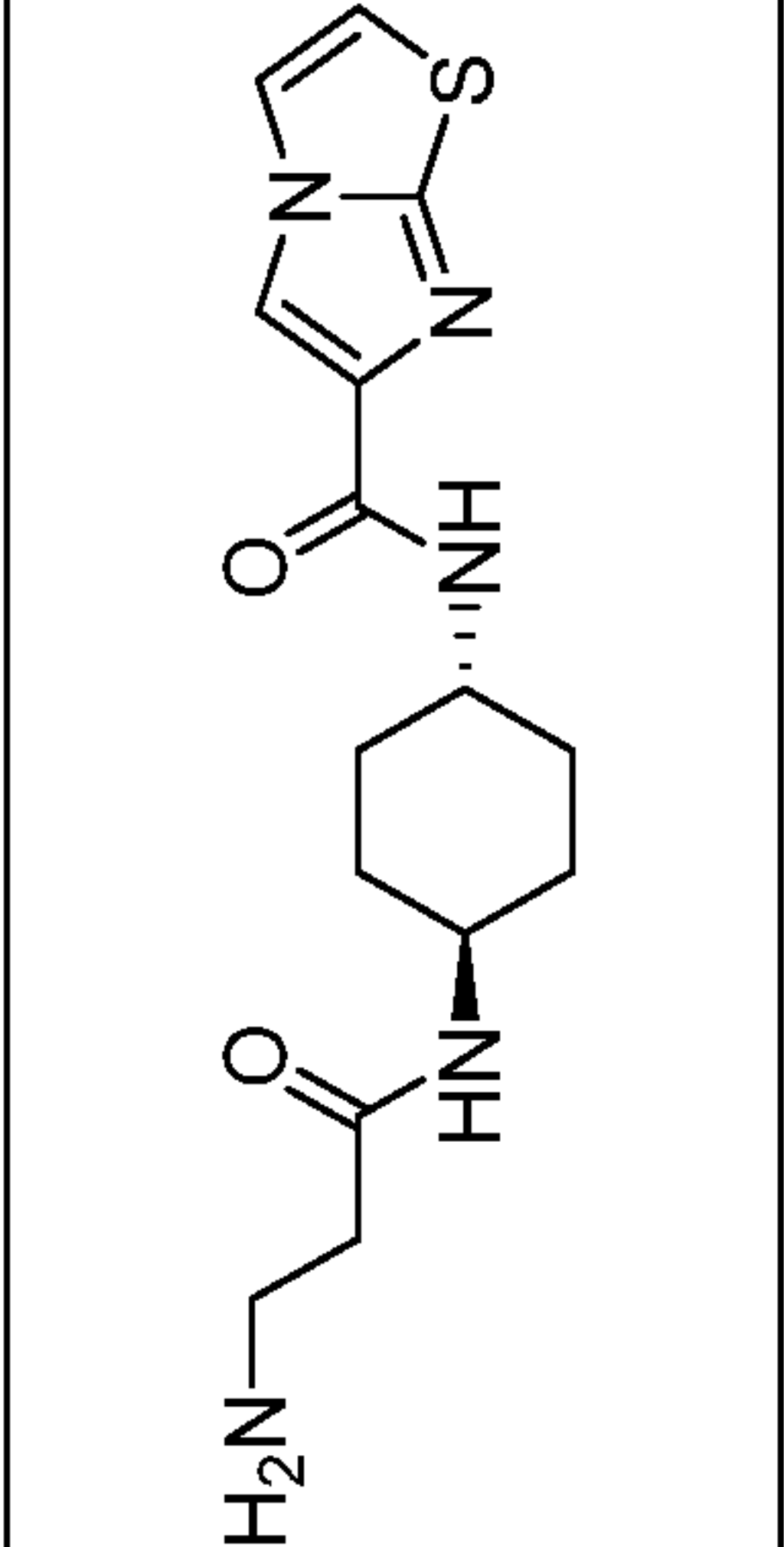
5		None	292		None
6		None	293		None
7			294		HCl
8		None	295		TFA

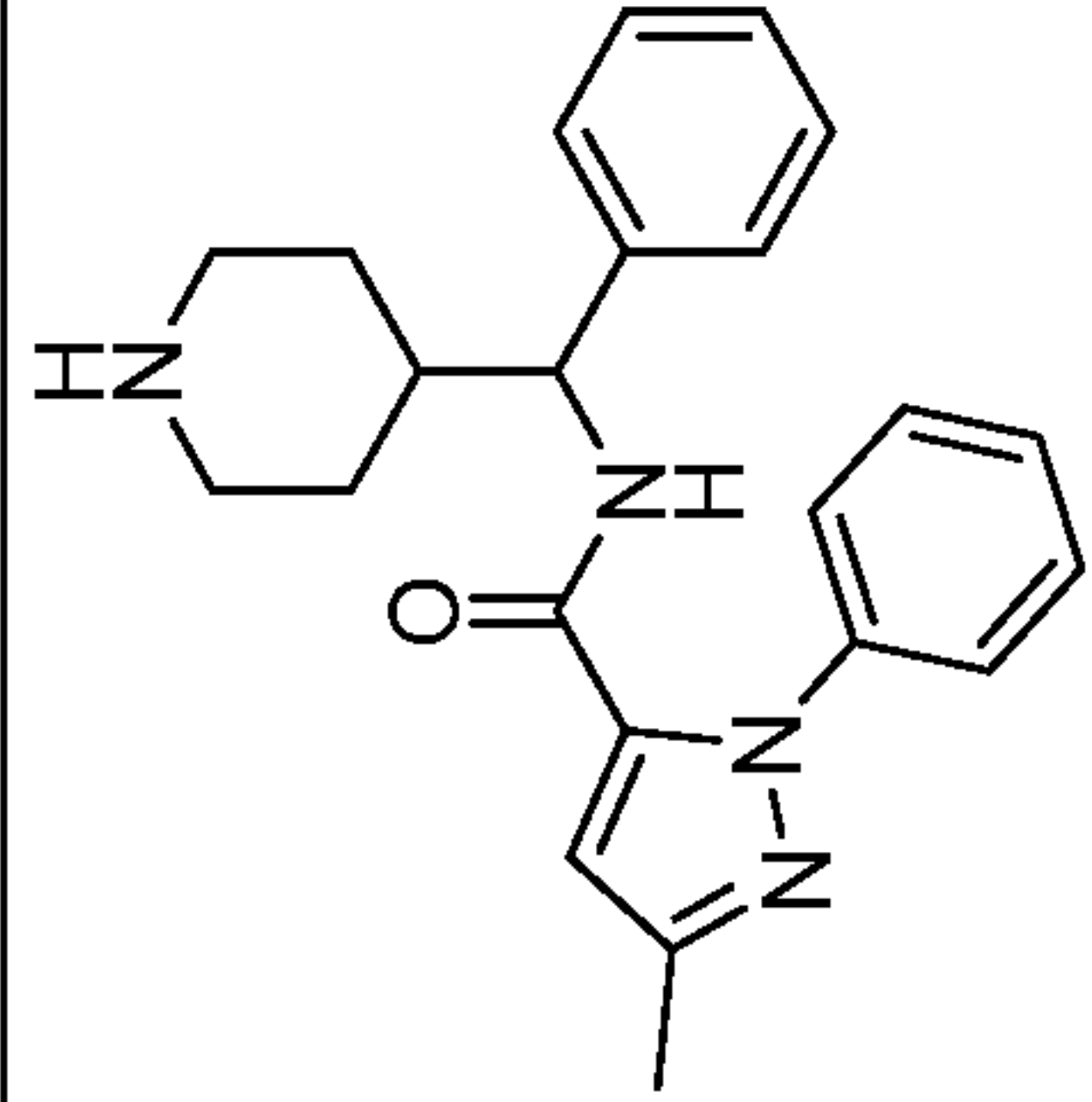
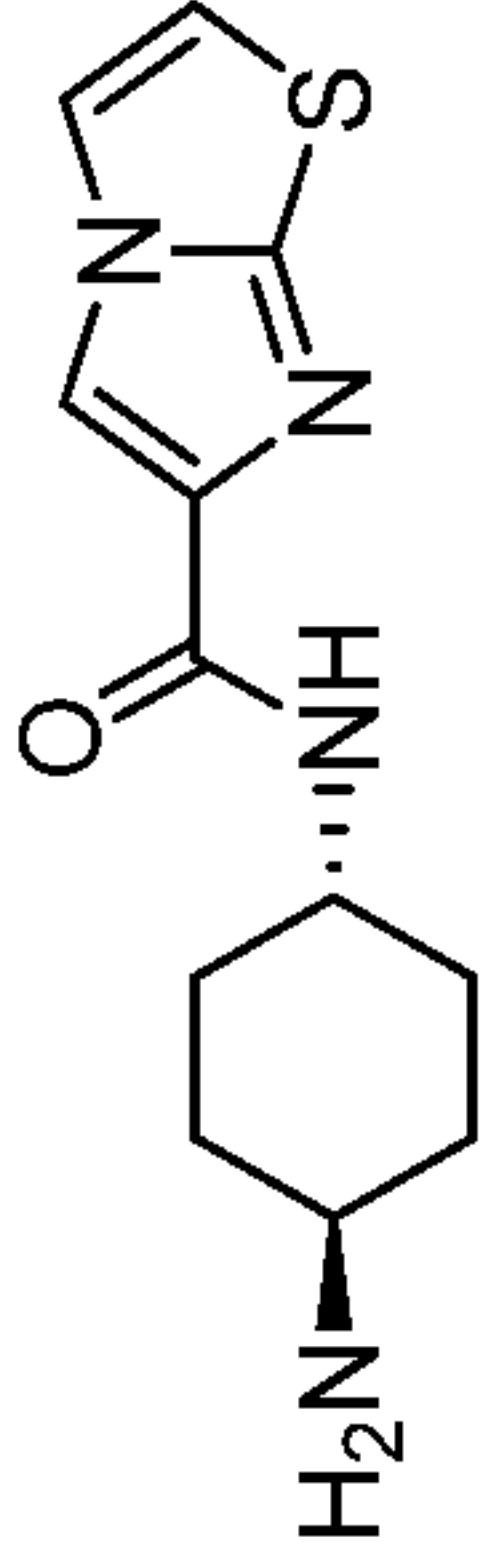
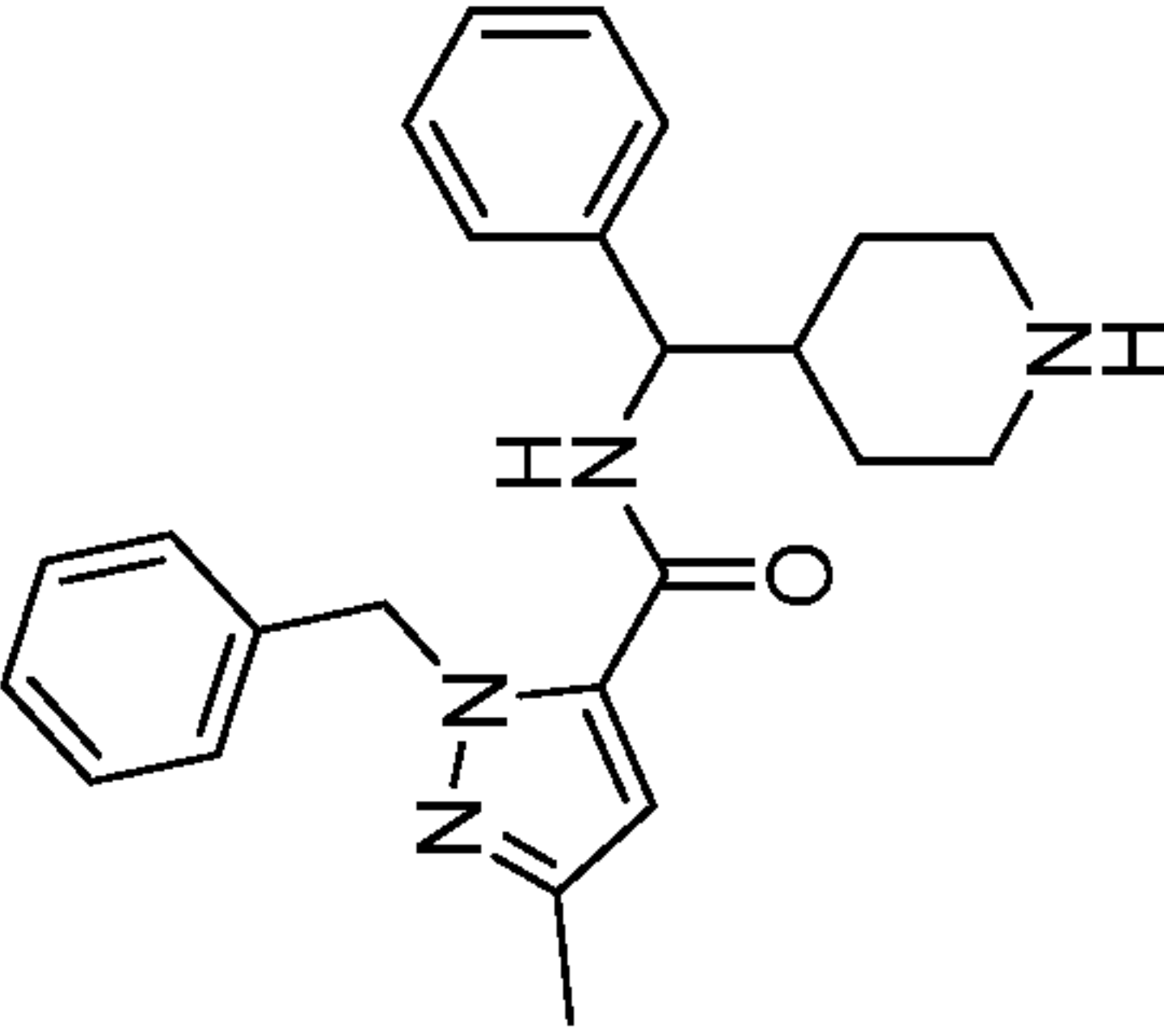
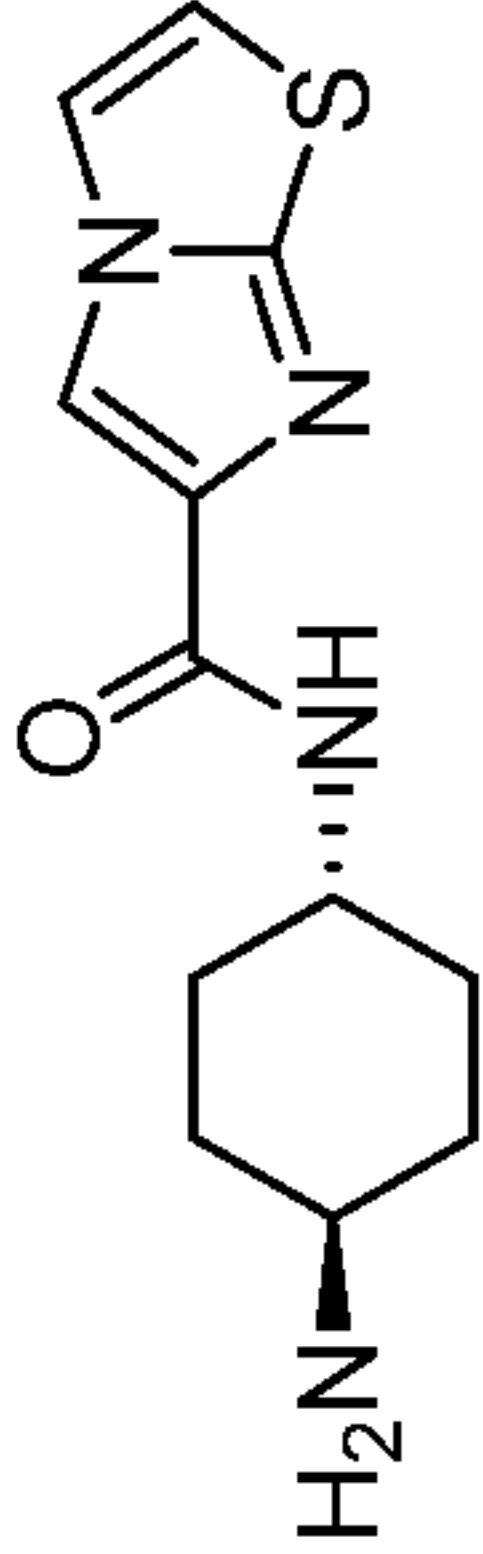
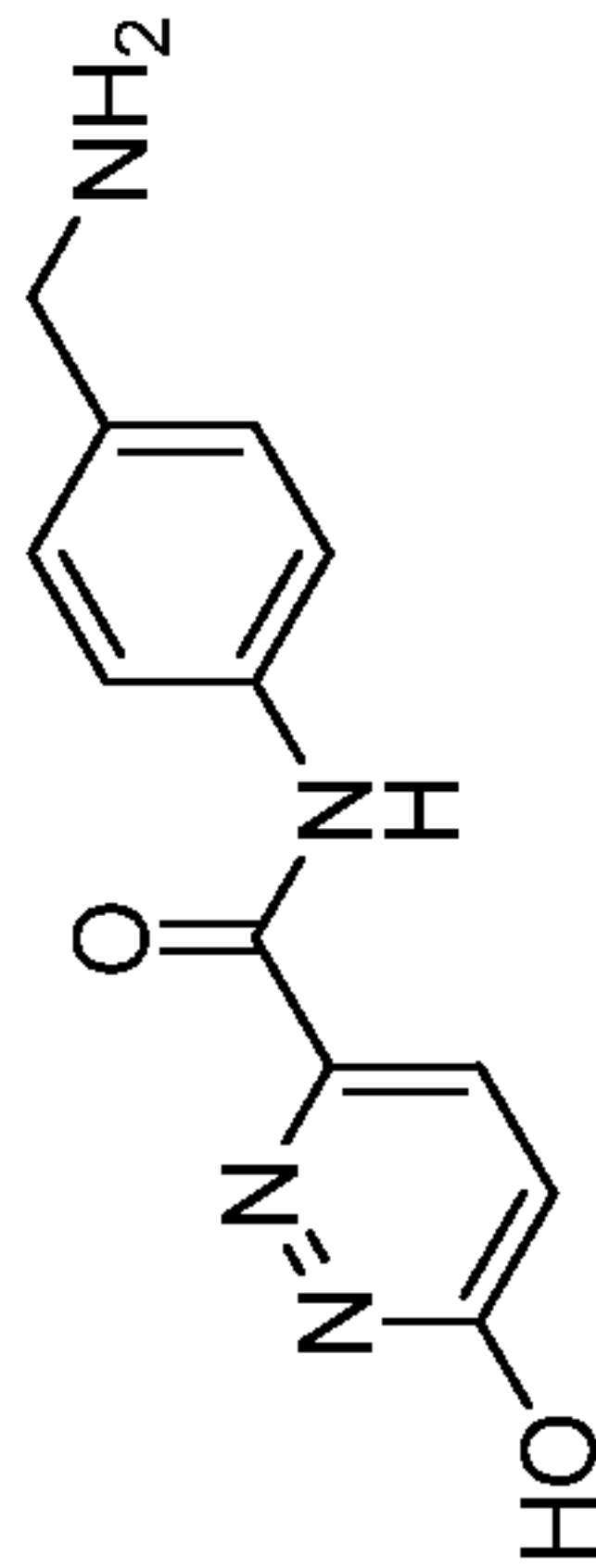
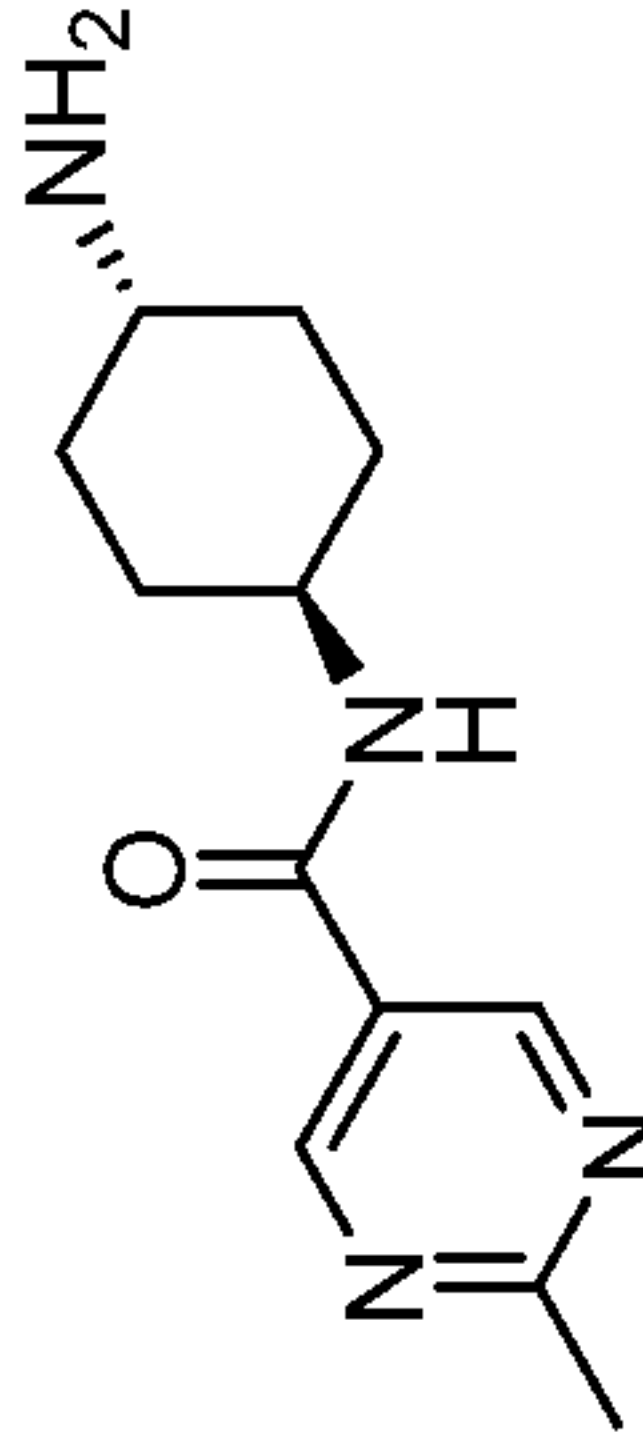
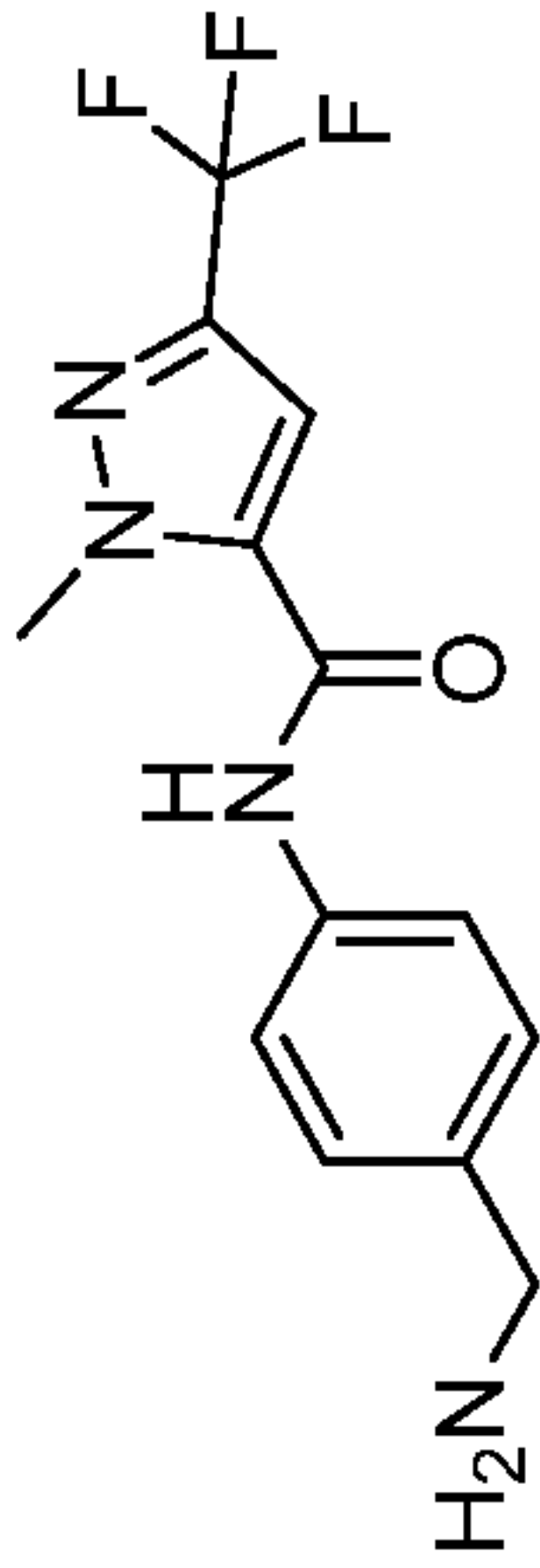
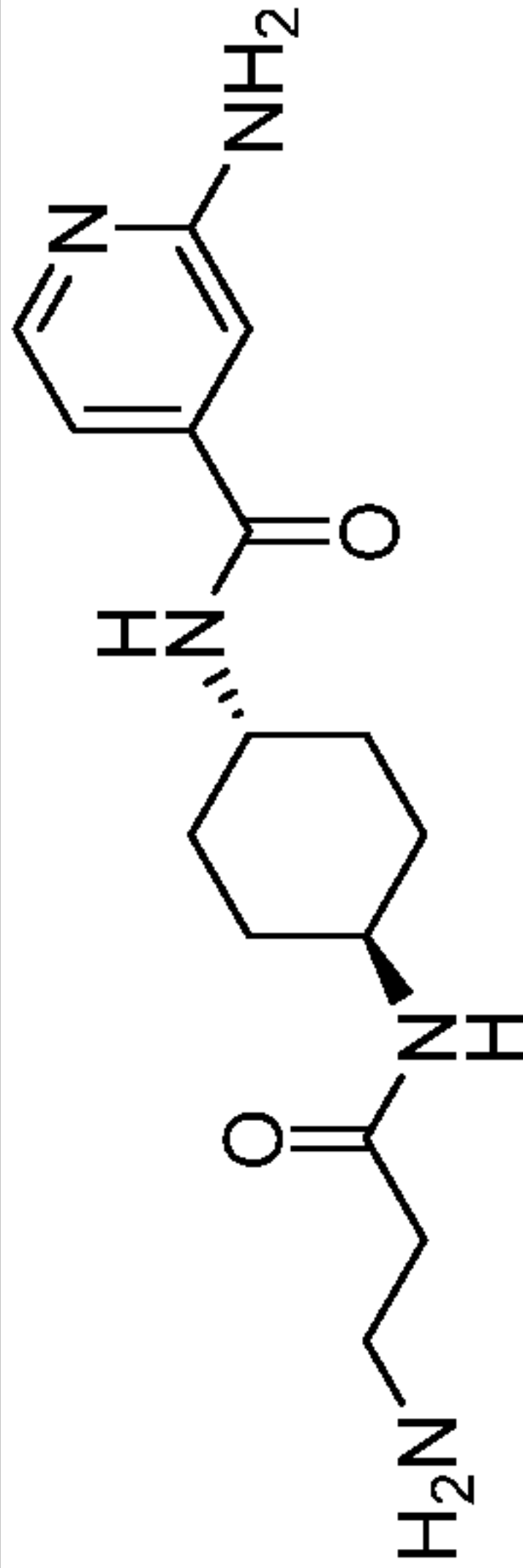
9		None	296		HCl
10		None	297		HCl
11		HCl	298		HCl
12		None	299		TFA

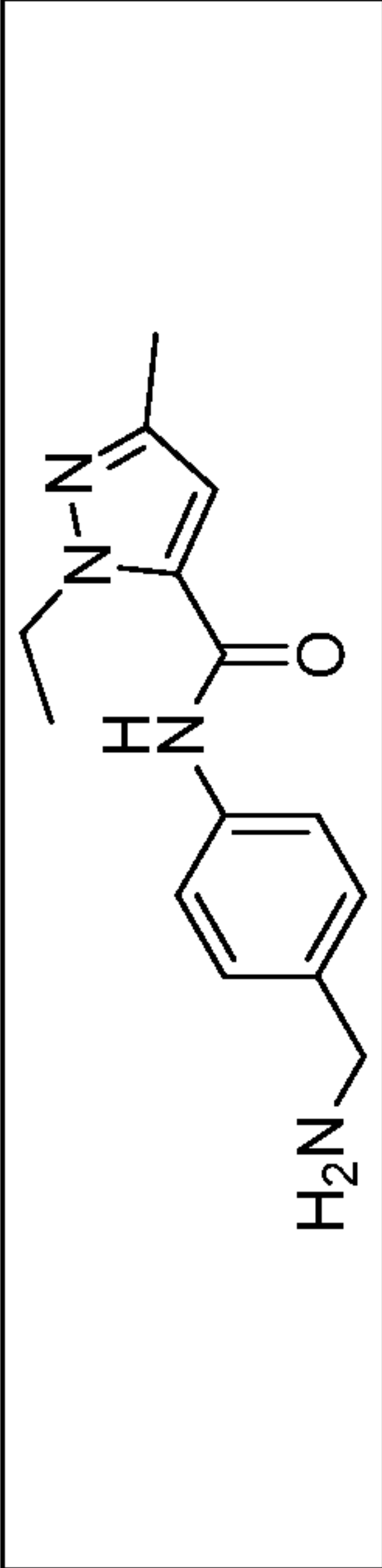
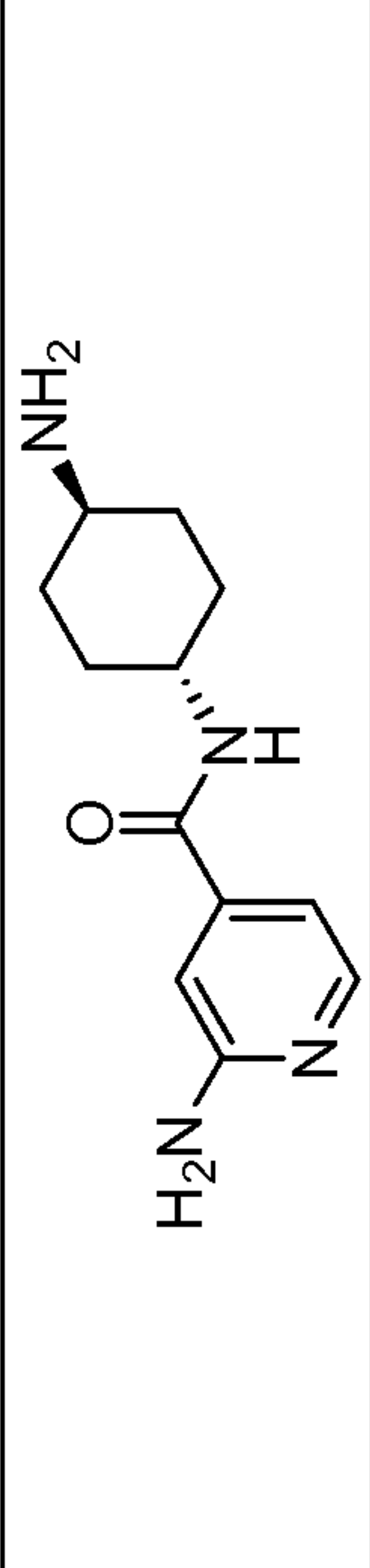
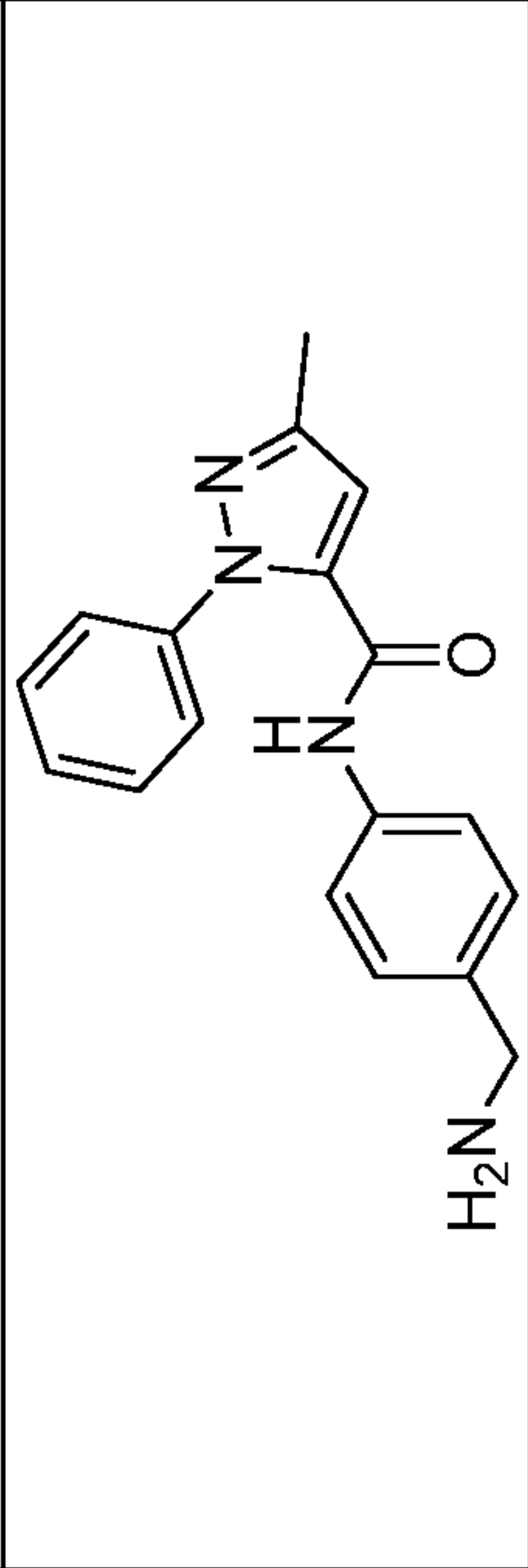
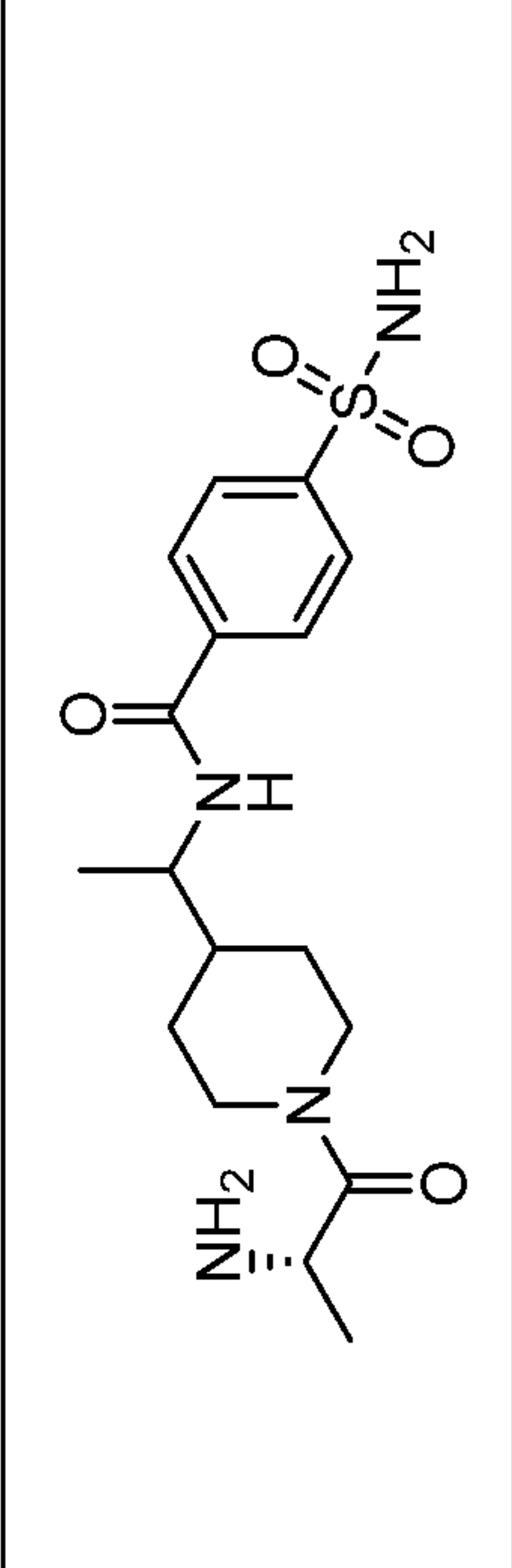
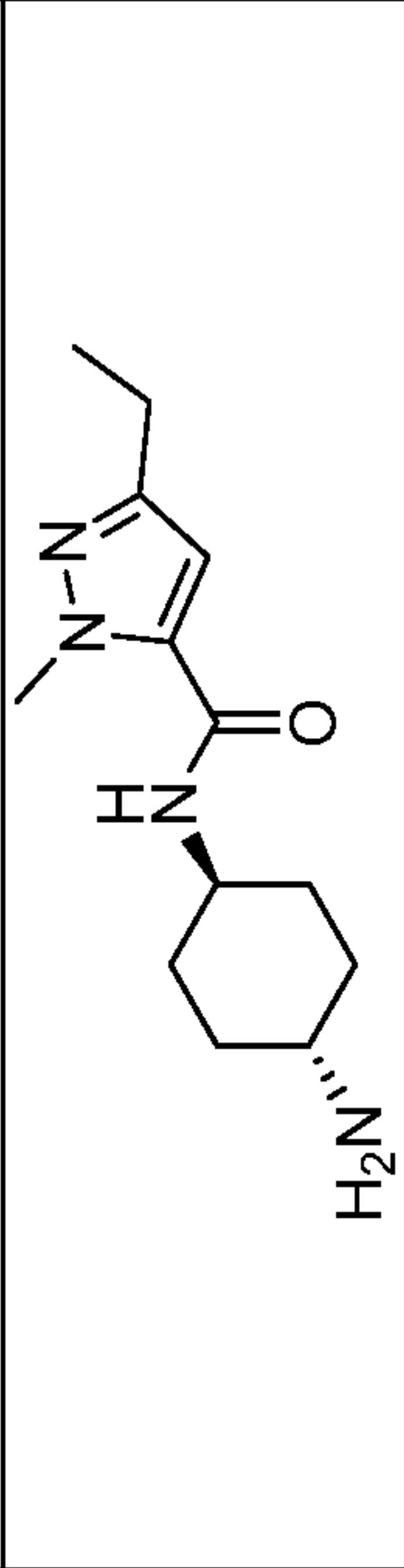
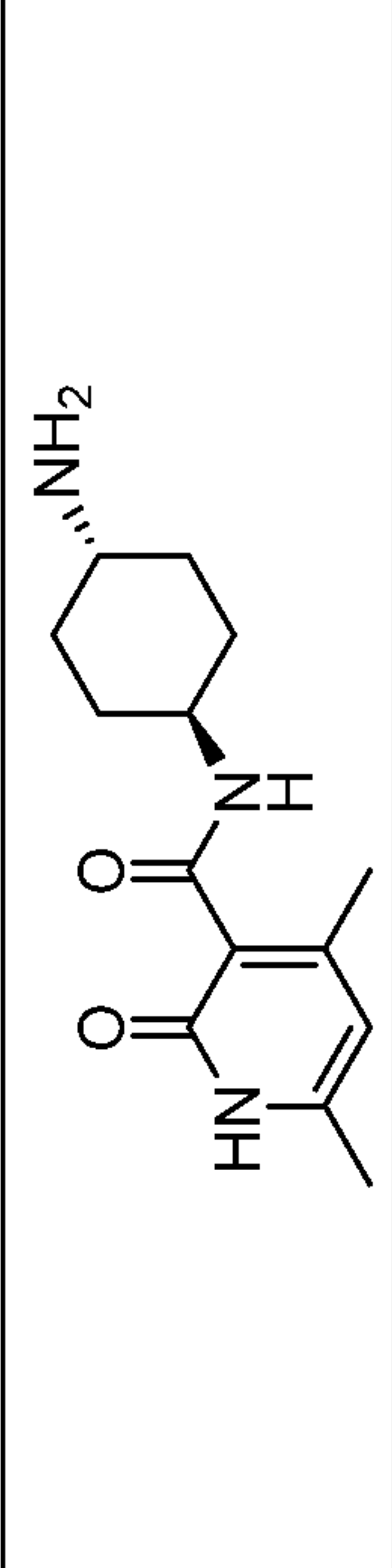
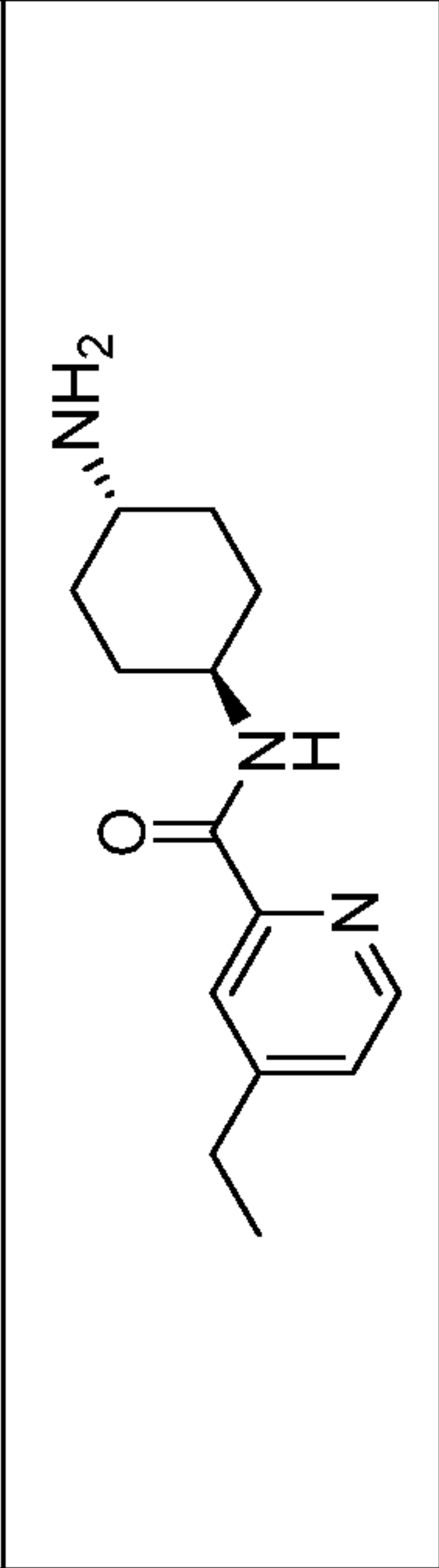
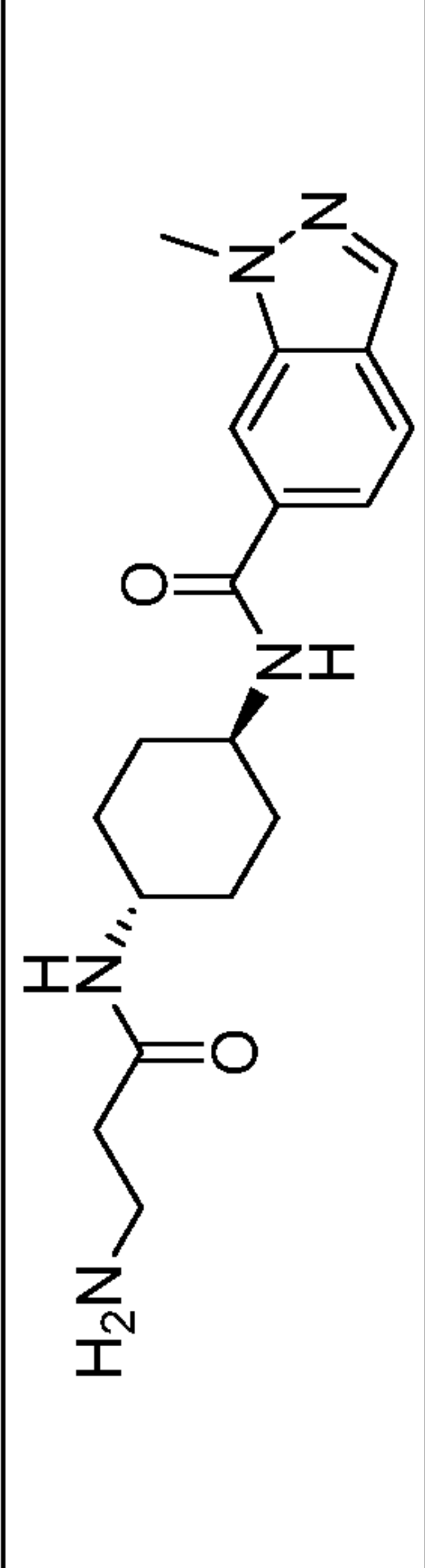
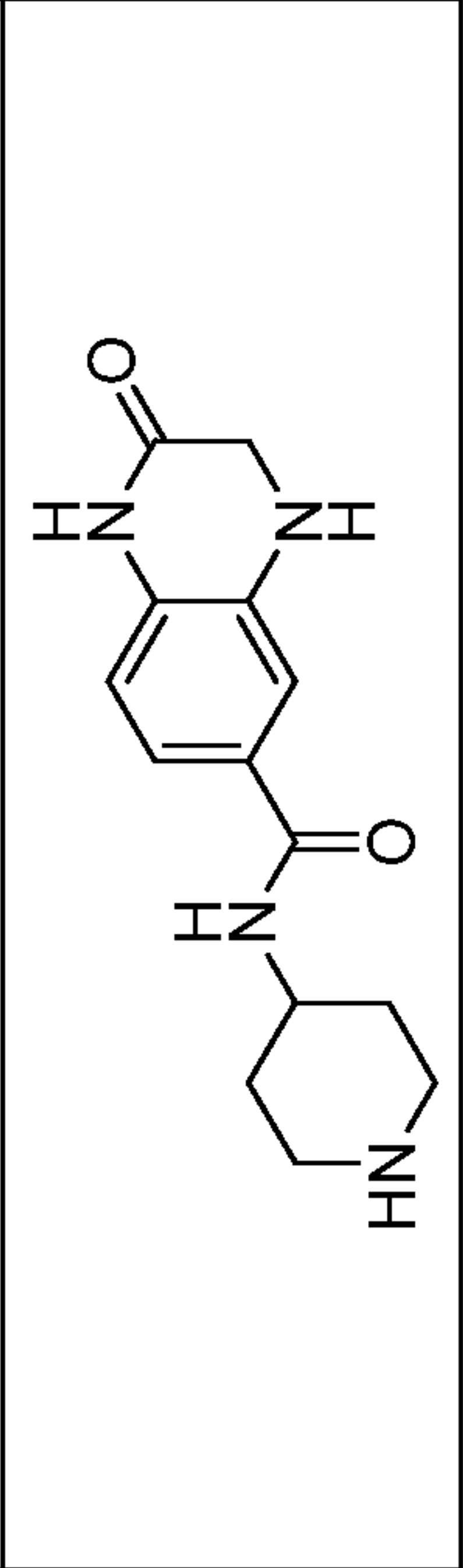
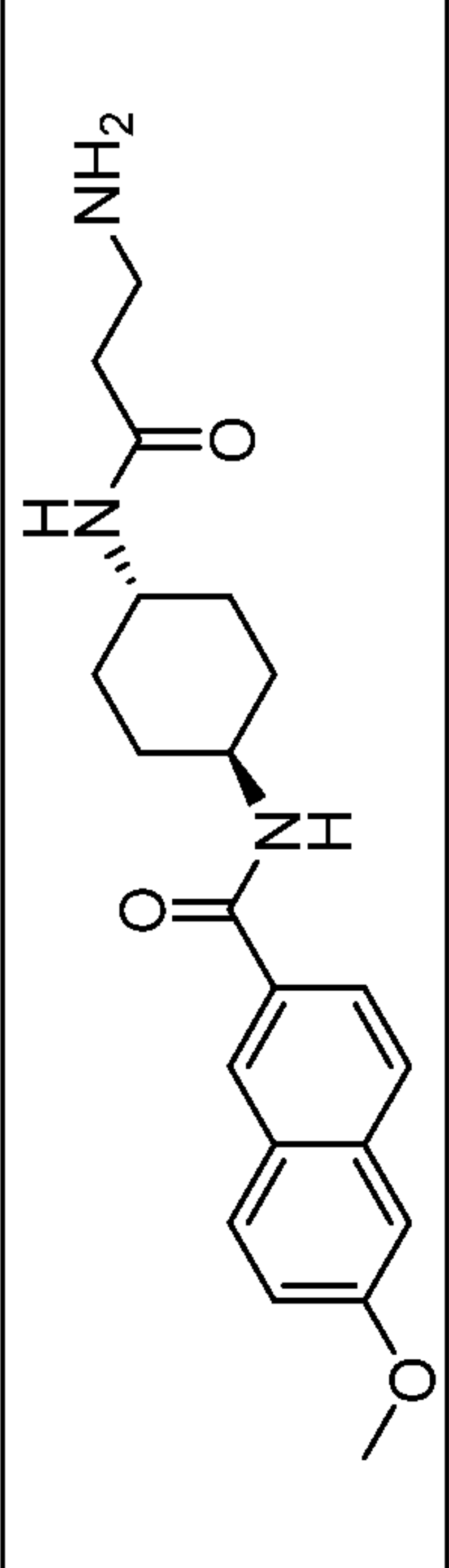
13		HCl	300		TFA
14		HCl	301		TFA
15		HCl	302		TFA
16		HCl	303		HCl
17		HCl	304		HCl

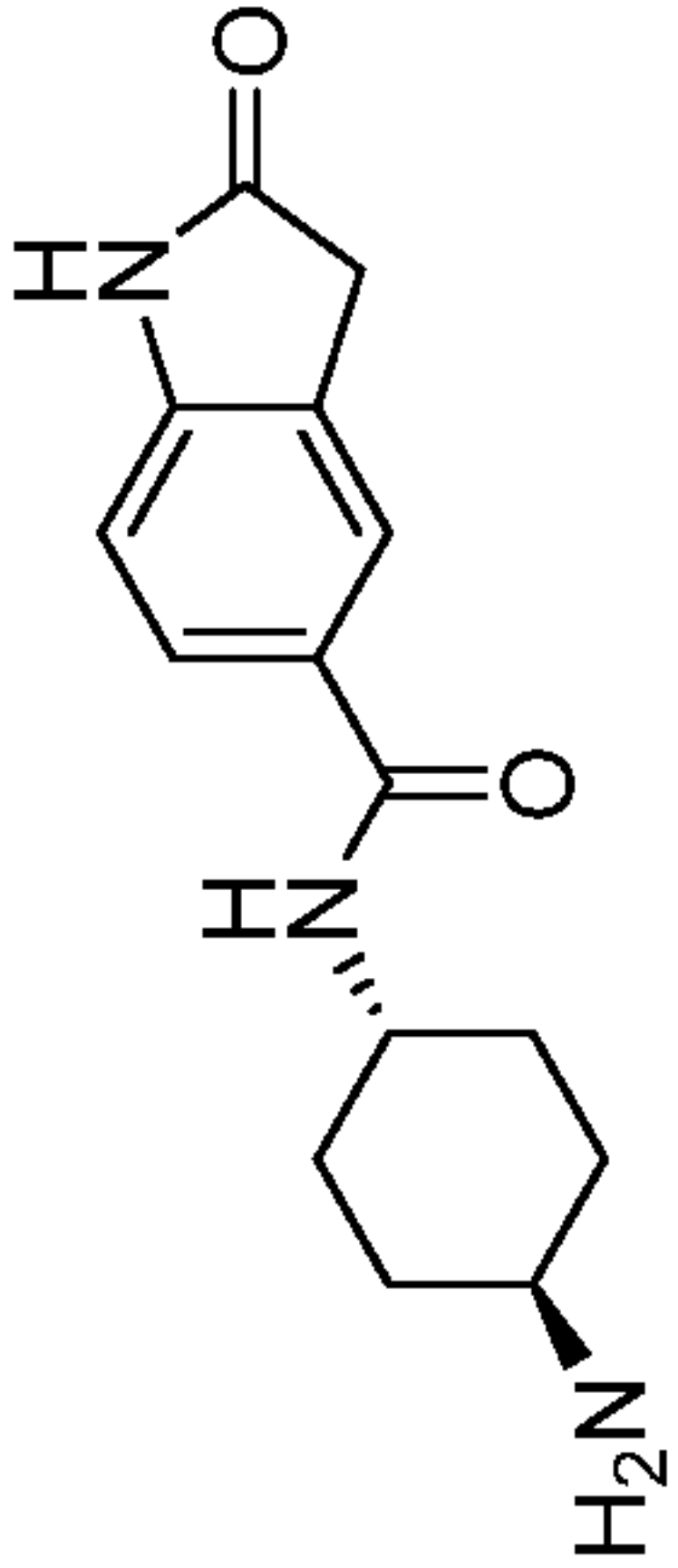
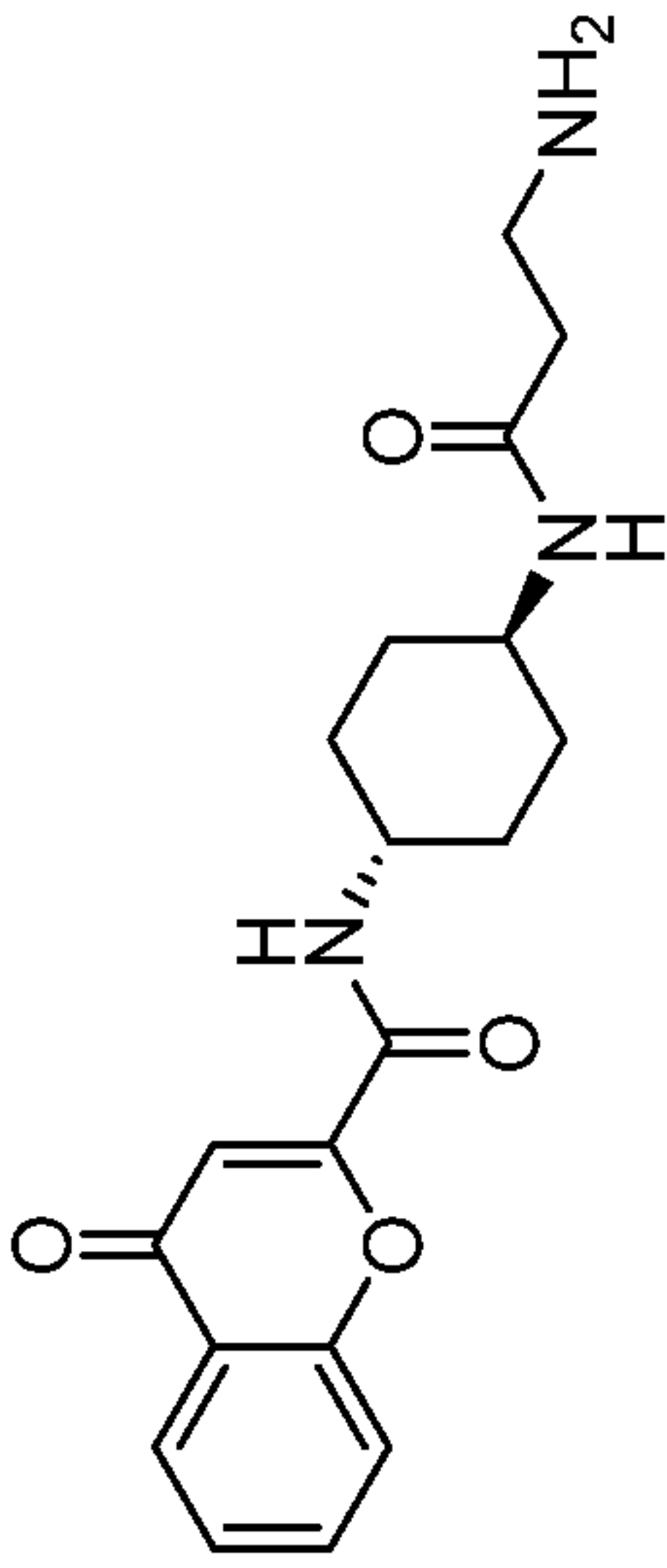
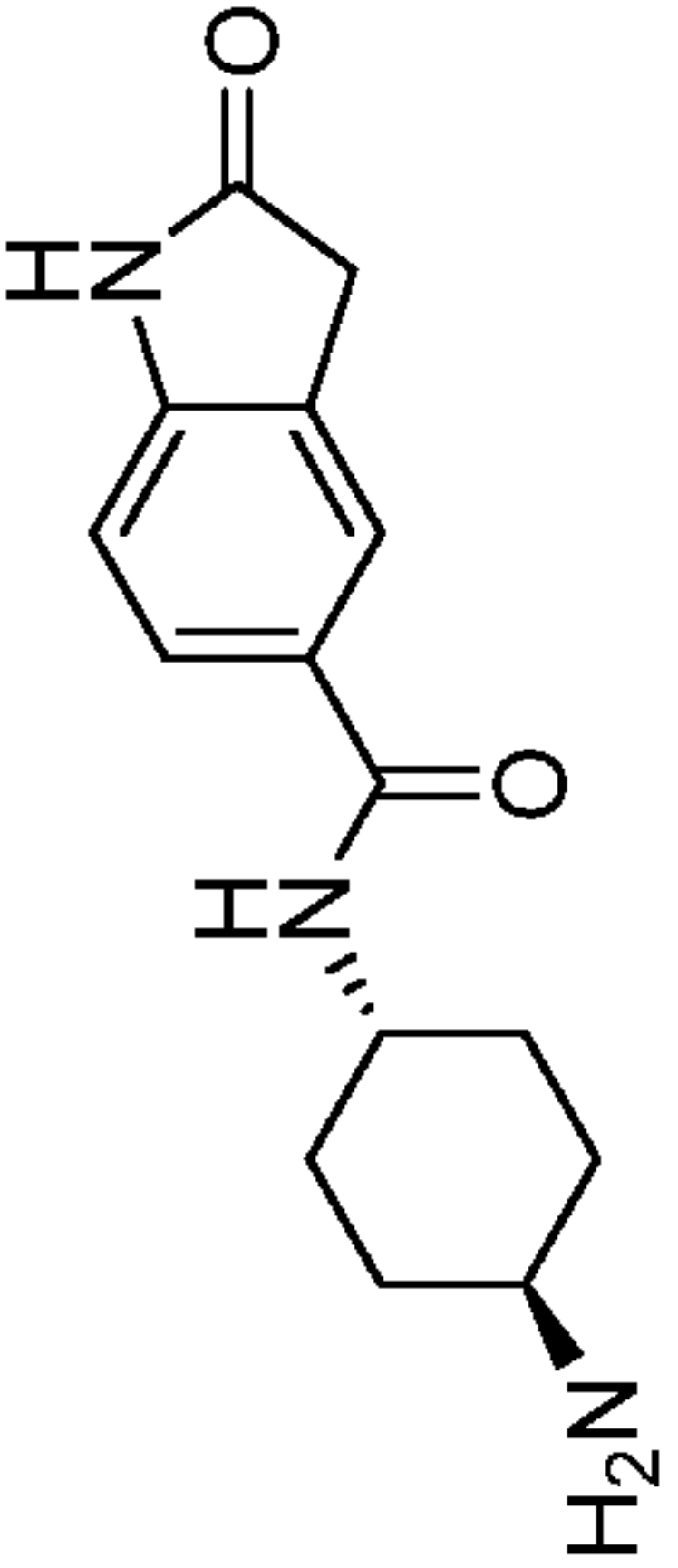
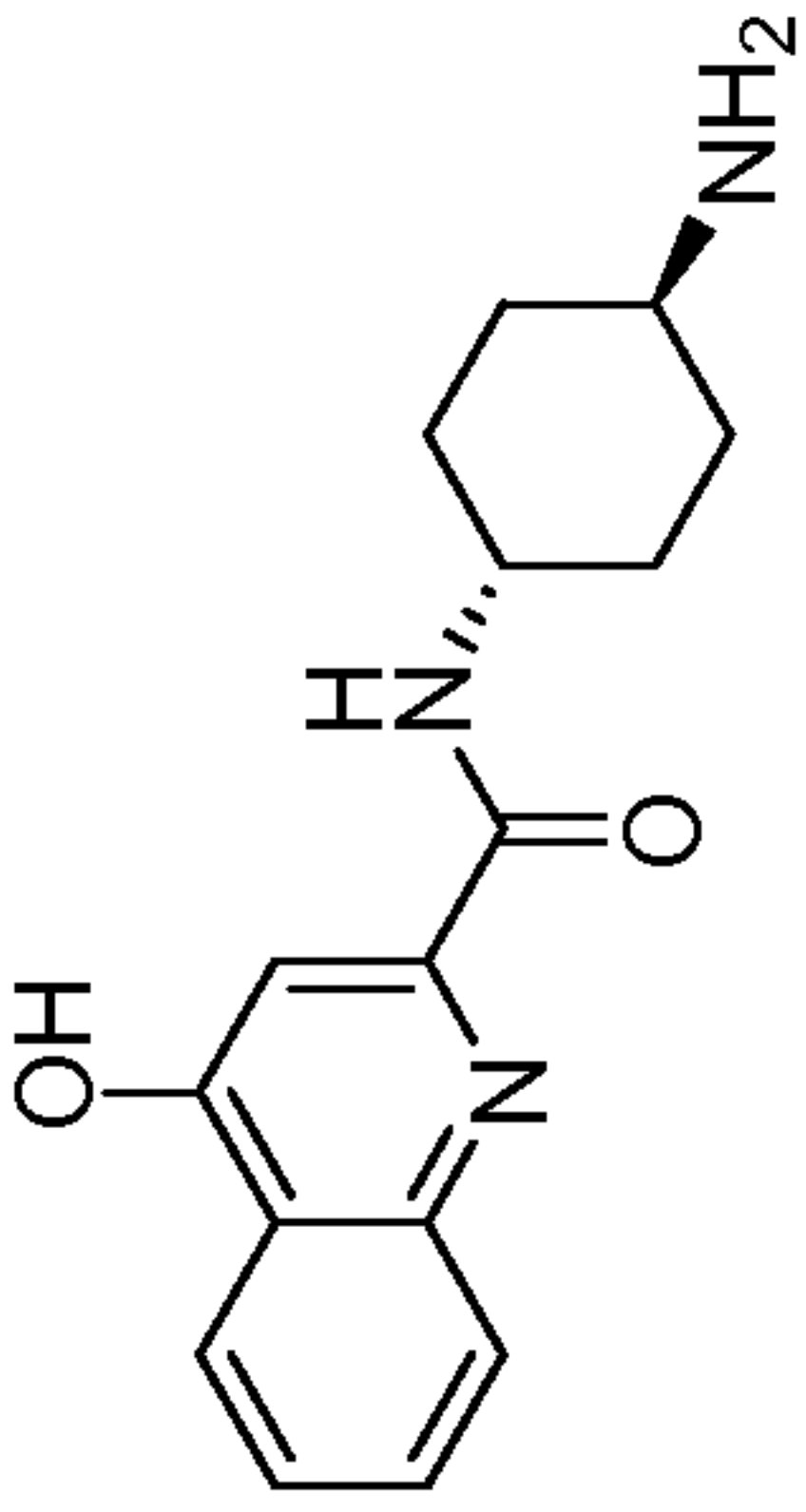
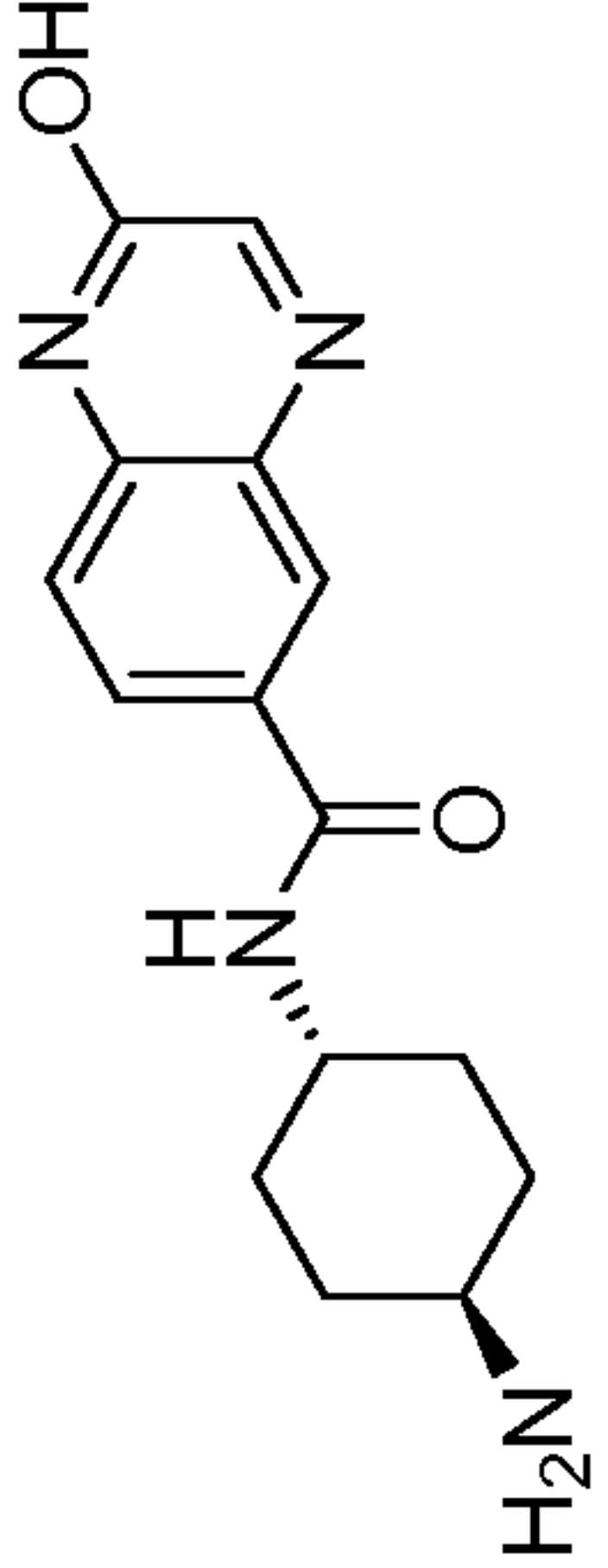
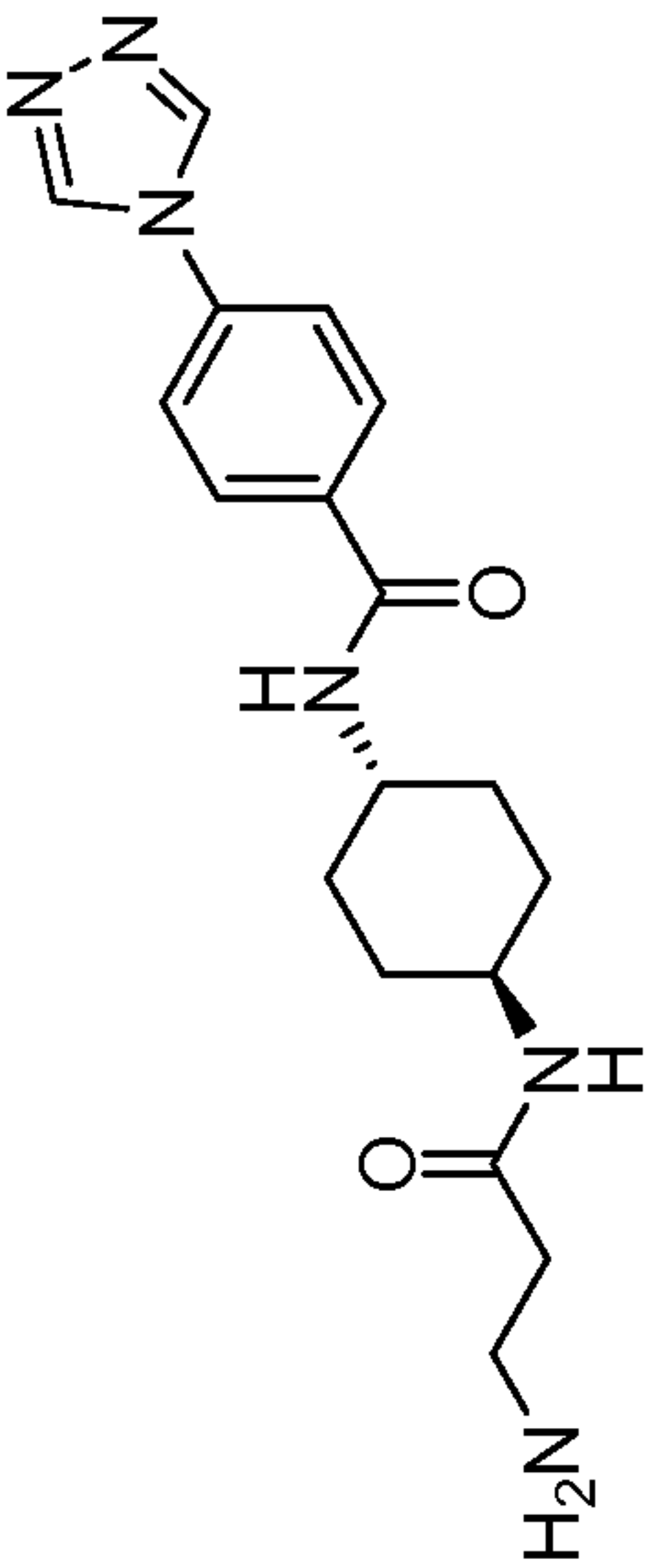
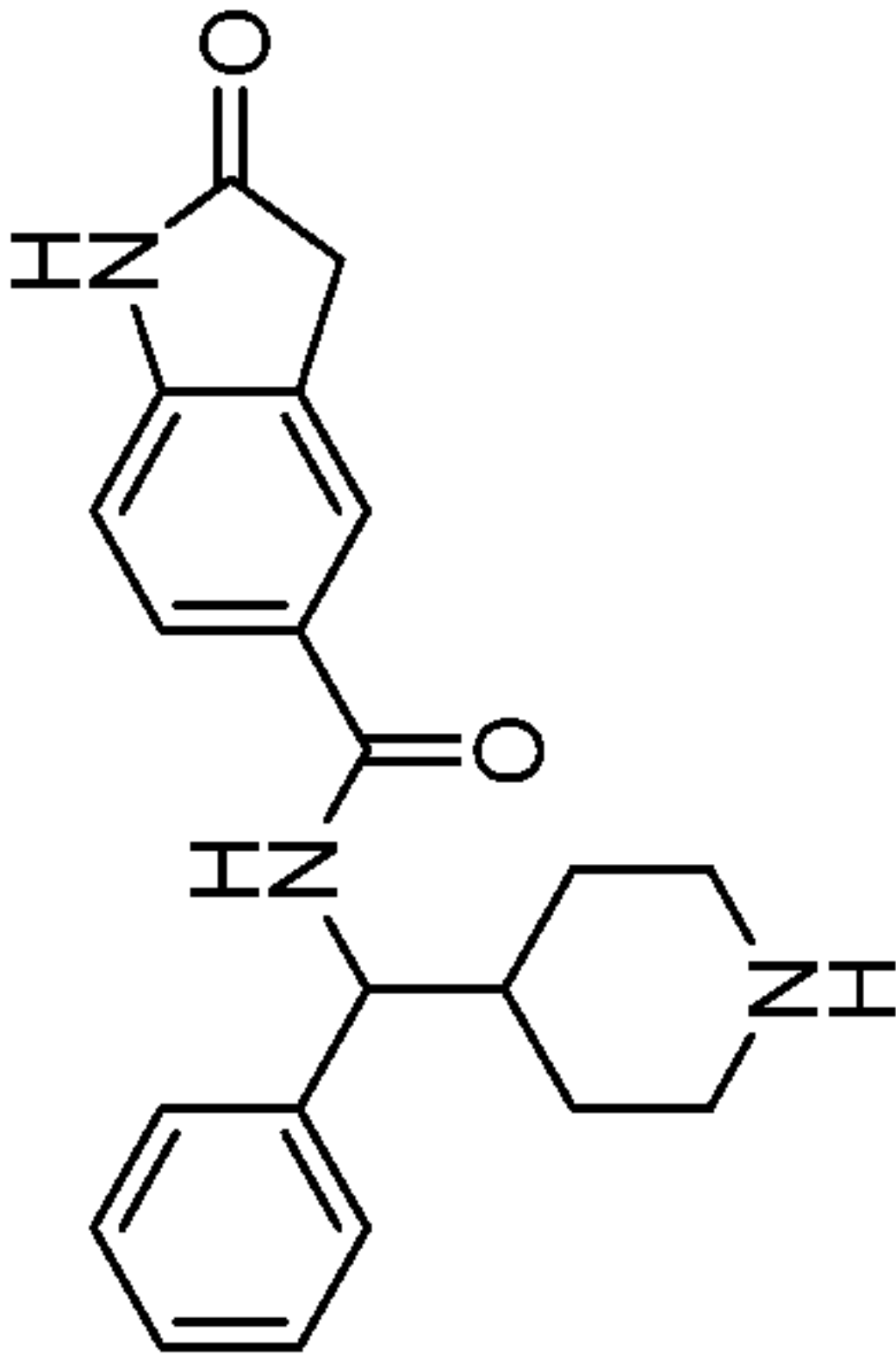
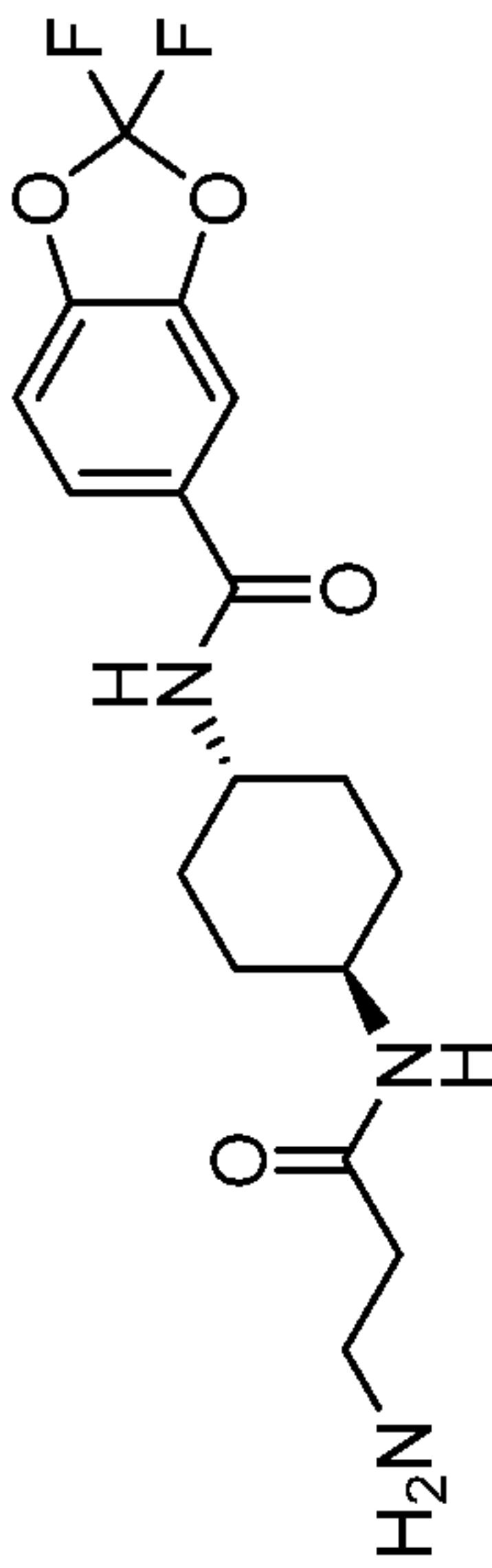
18		TFA	305		TFA
19		TFA	306		TFA
20		TFA	307		TFA
21		TFA	308		HCl
22		TFA	309		TFA

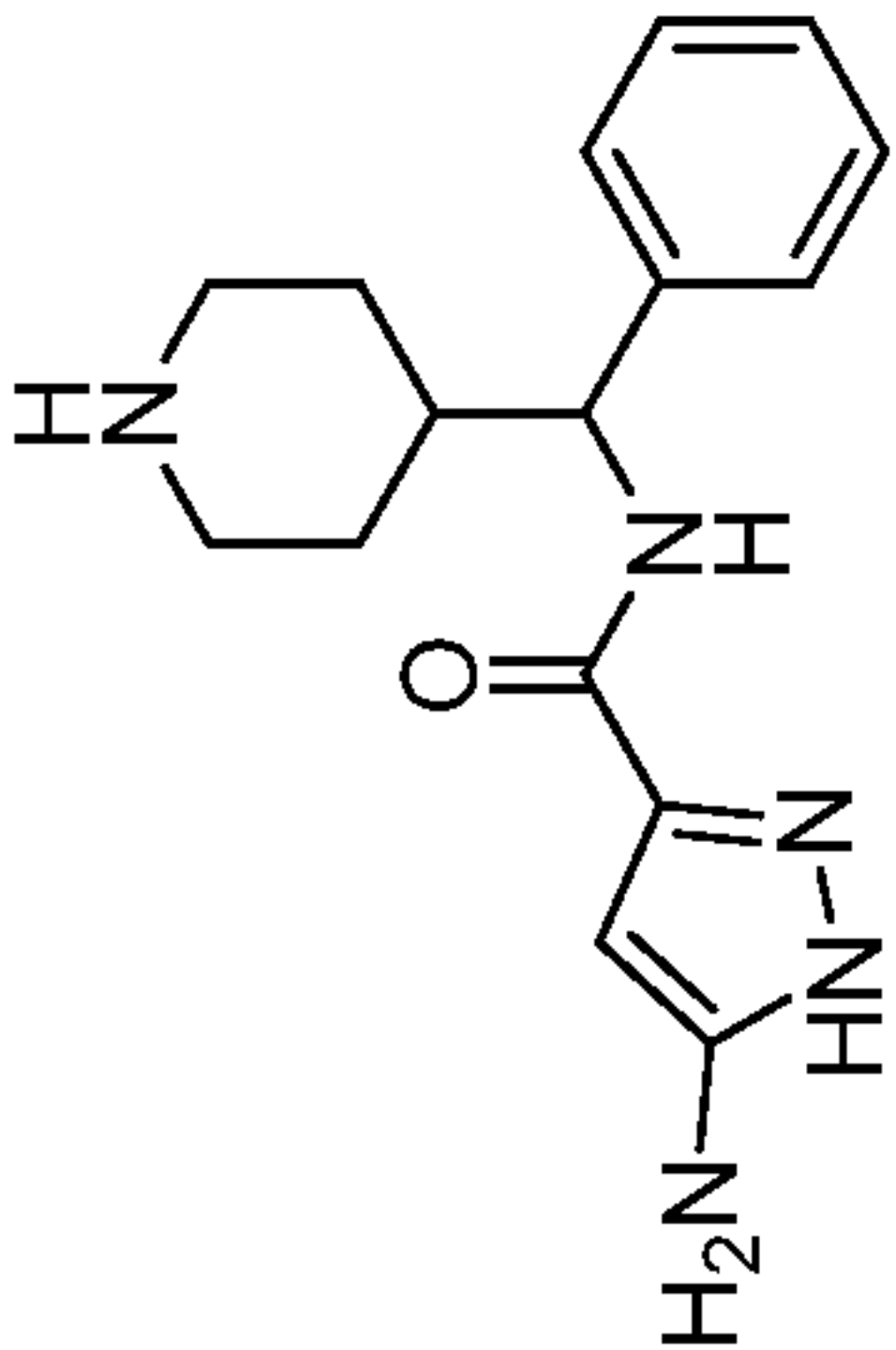
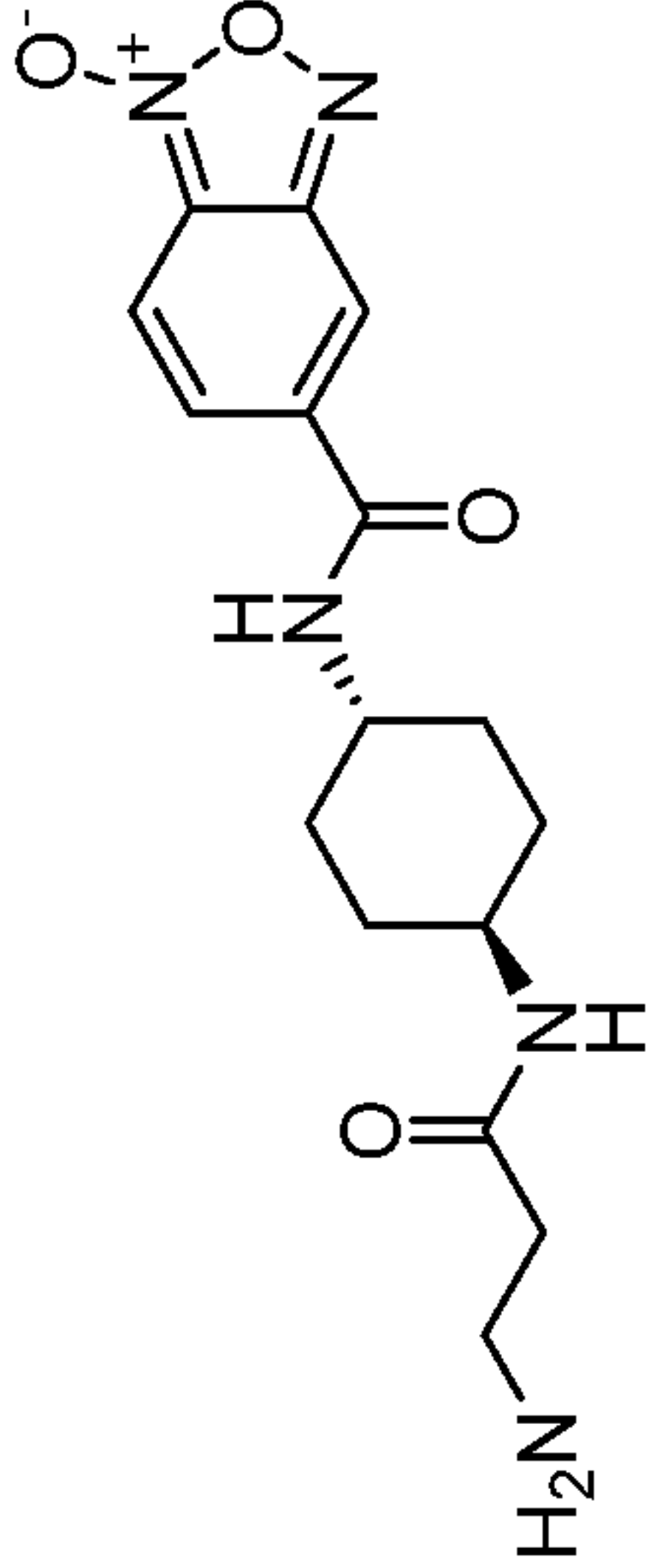
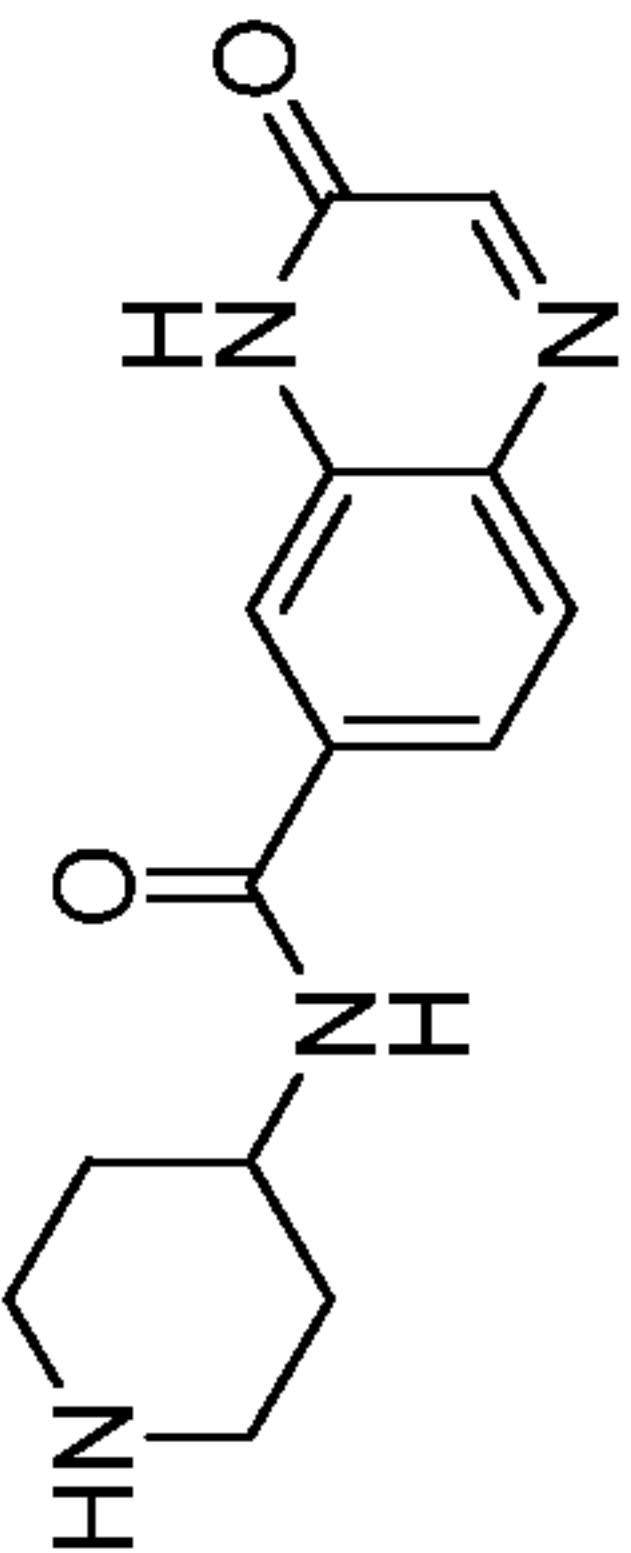
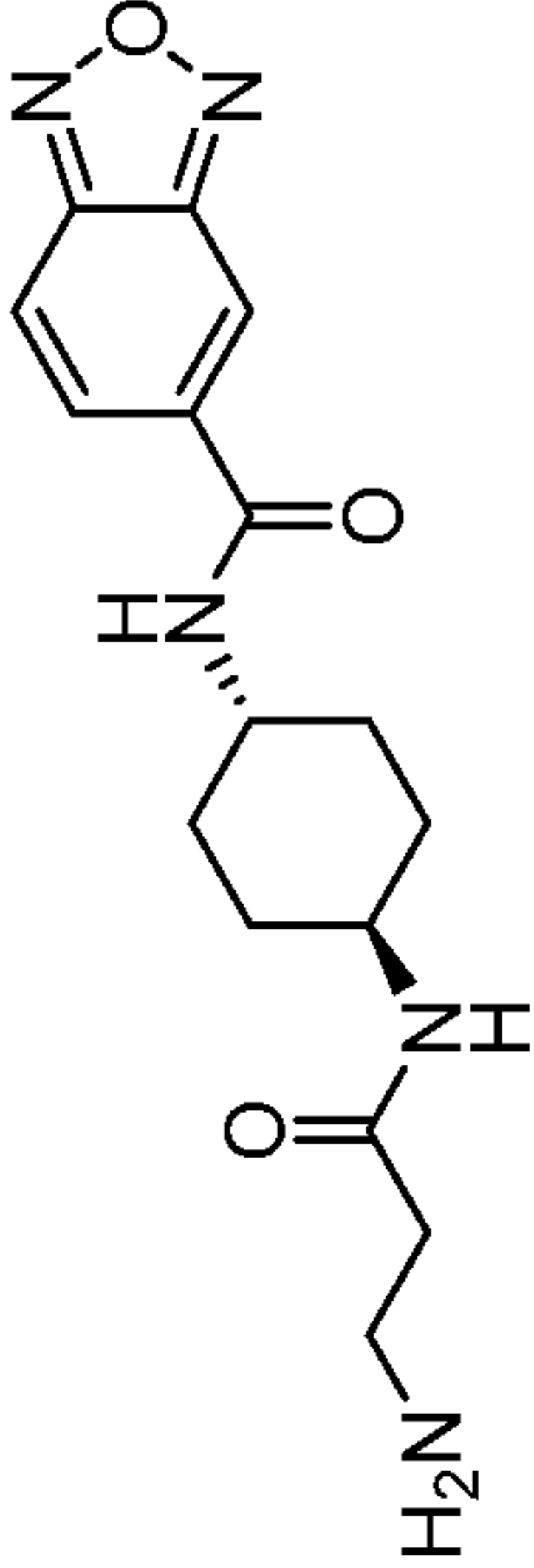
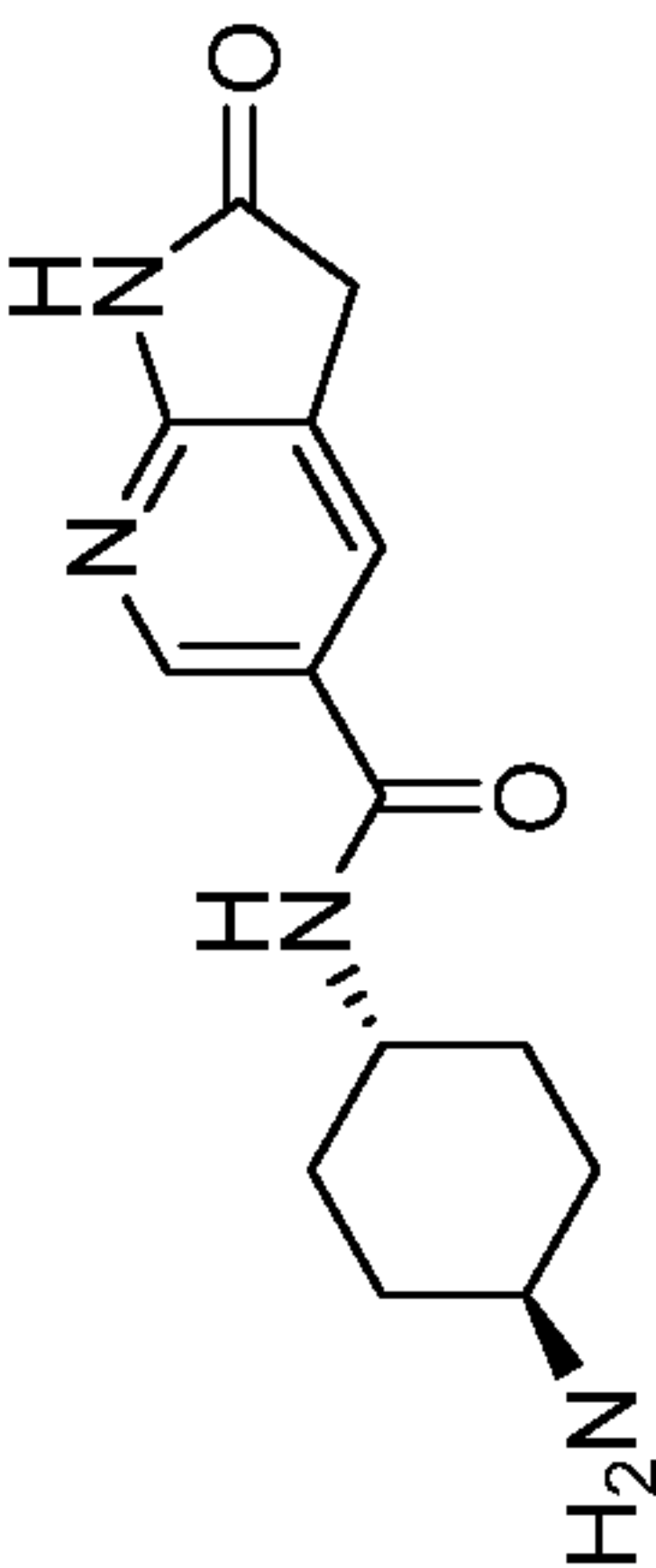
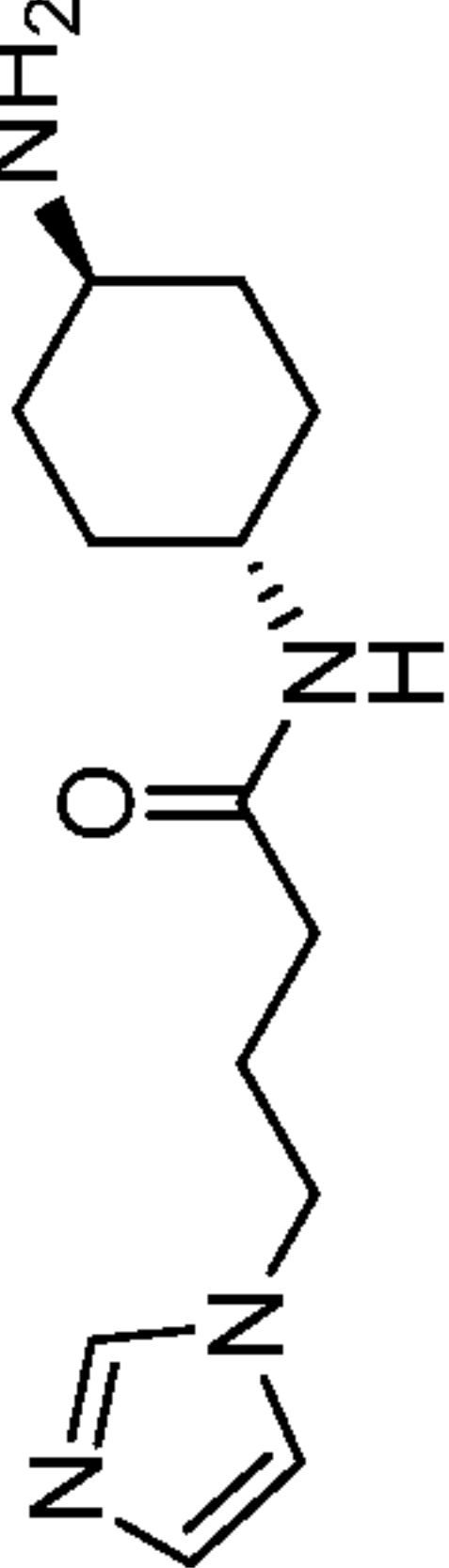
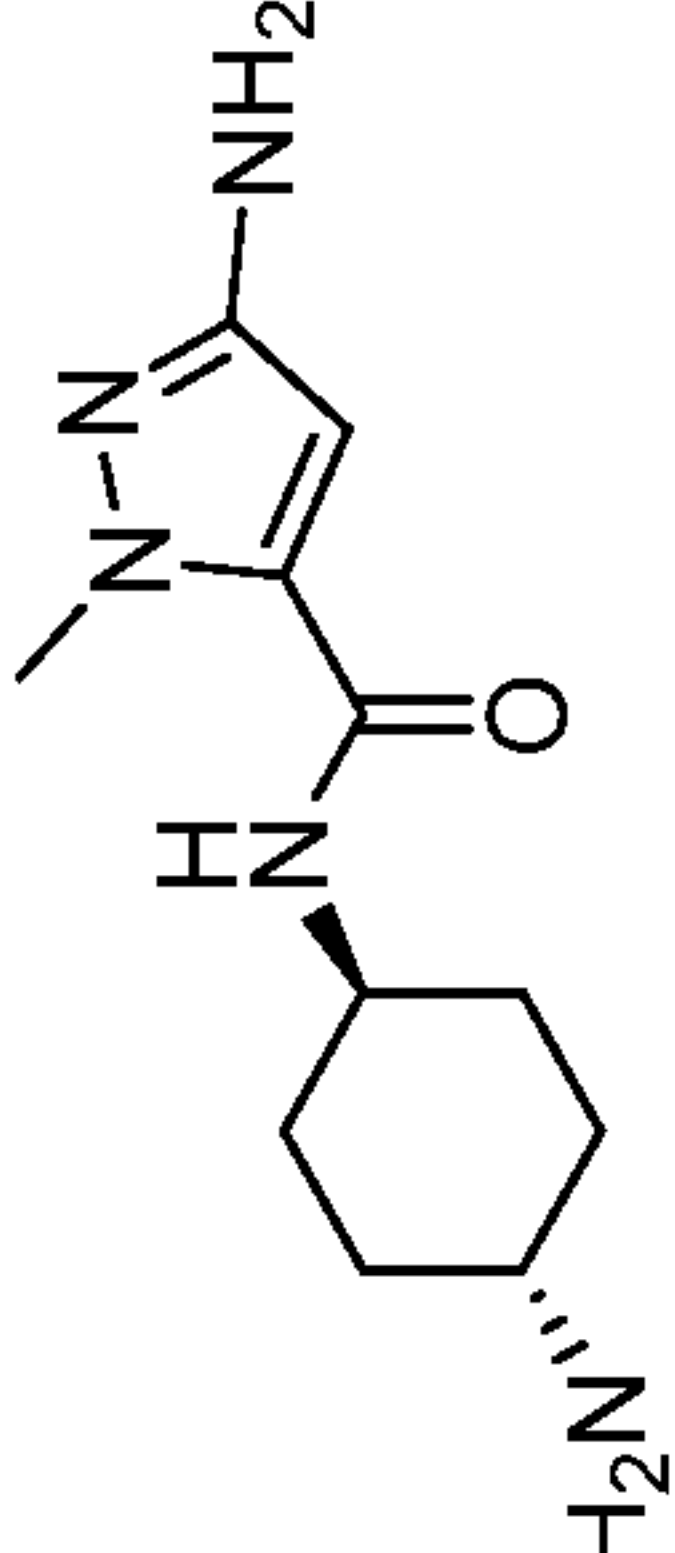
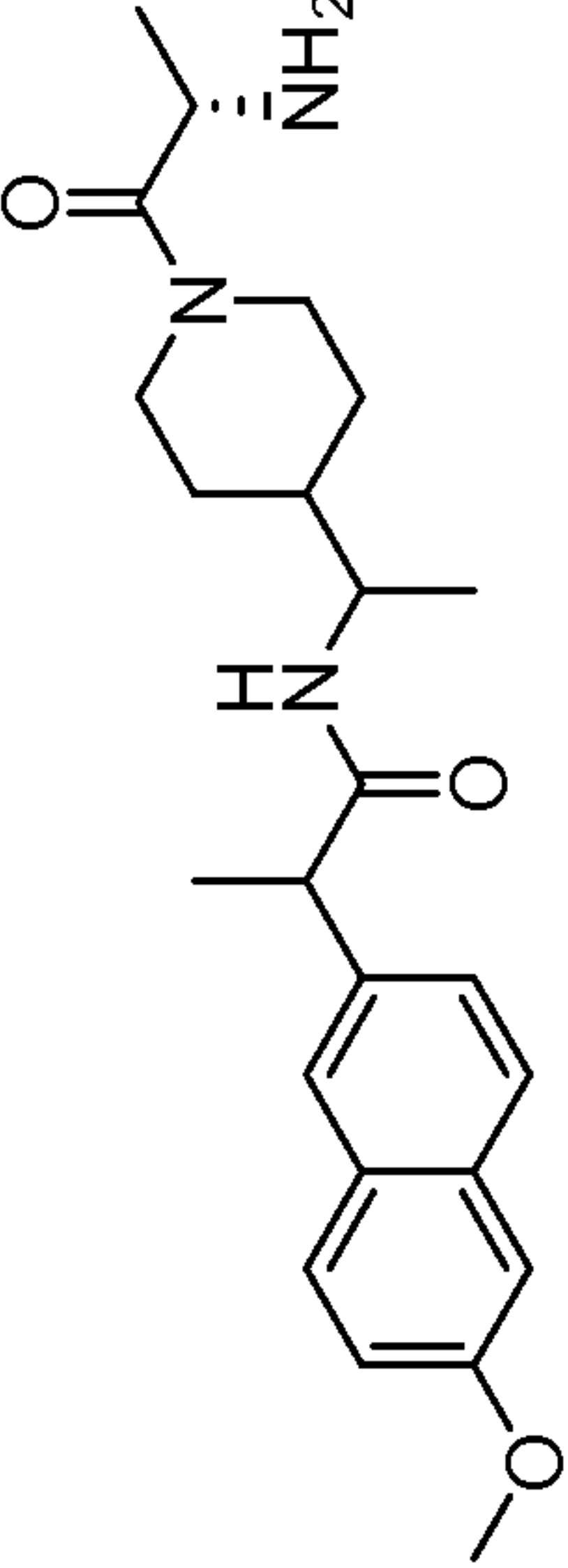
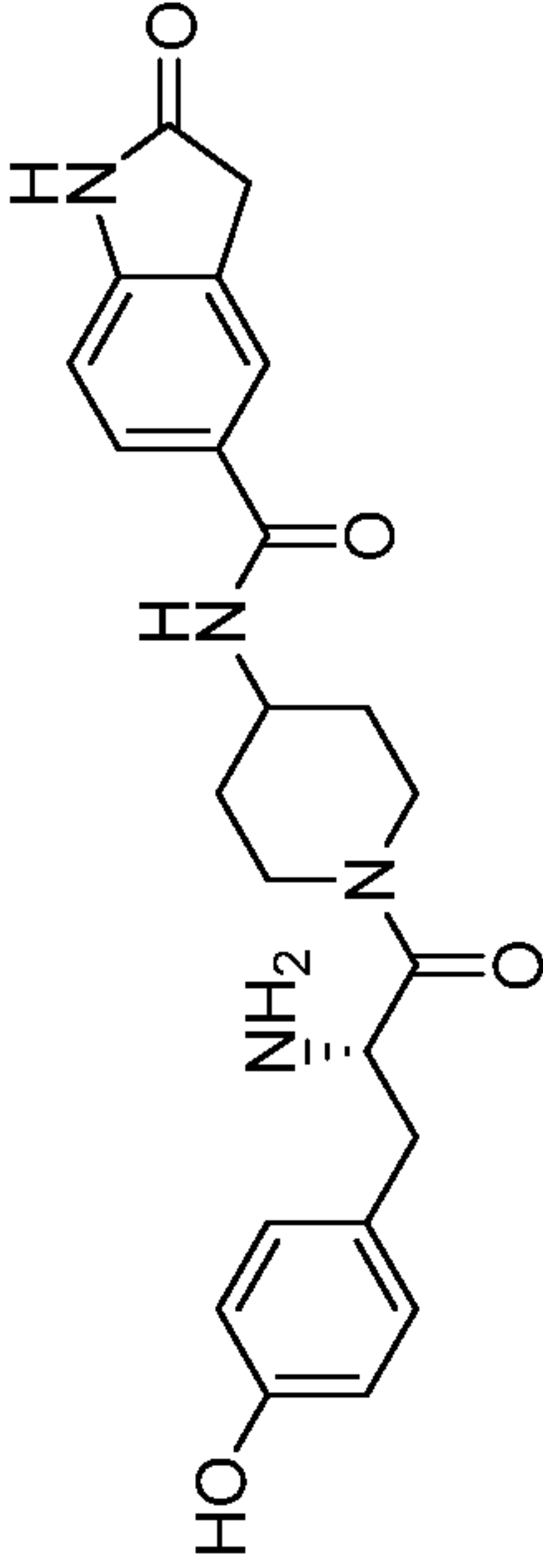
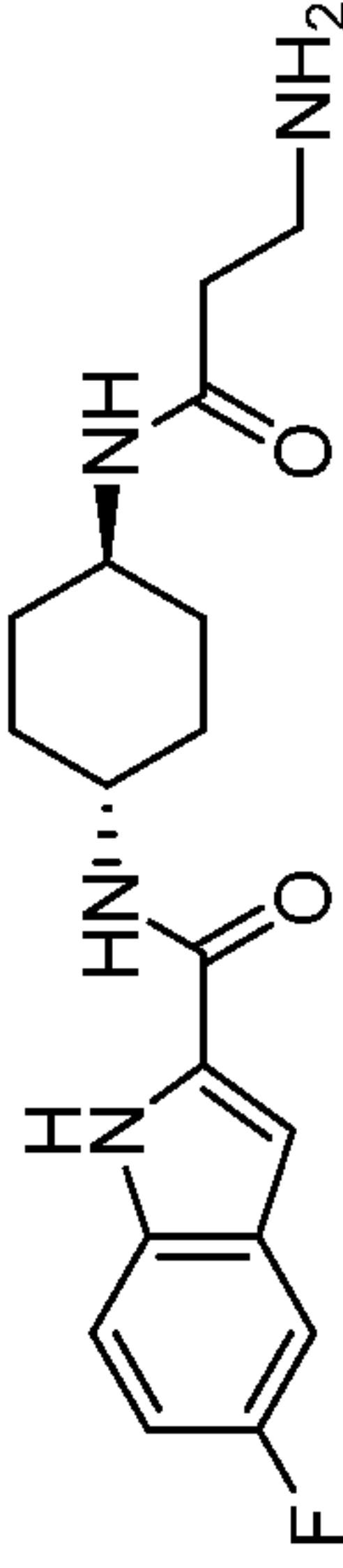
23		HCl	310		TFA
24		HCl	311		TFA
25		HCl	312		TFA
26		HCl	313		TFA
27		HCl	314		TFA

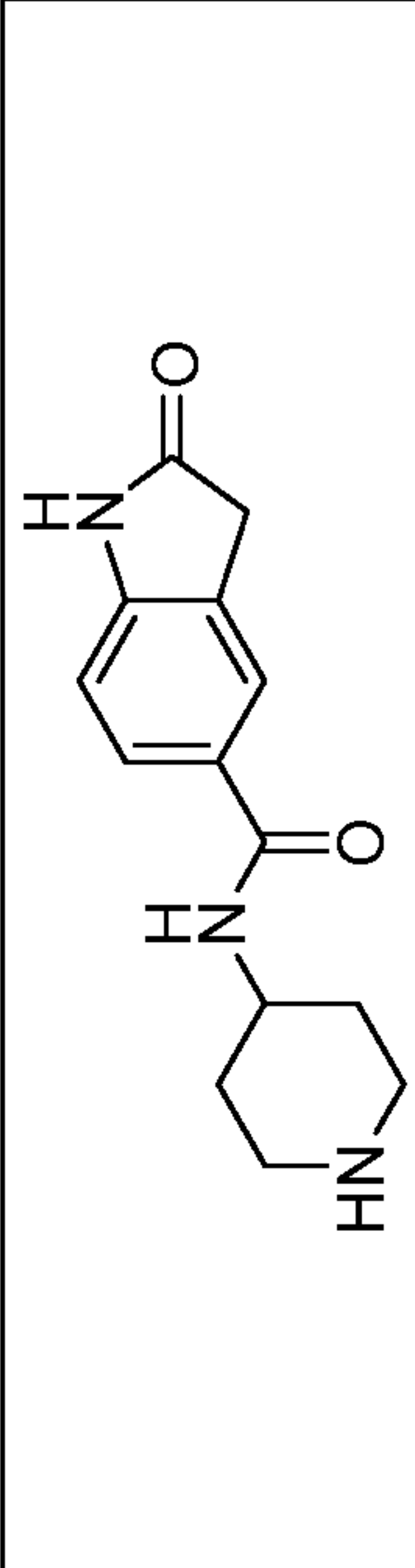
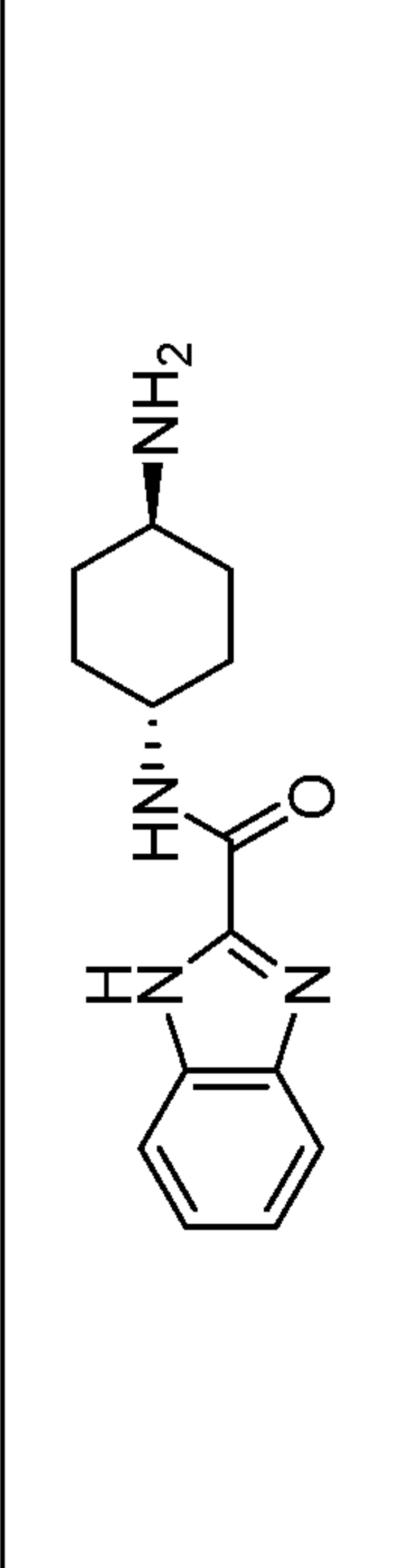
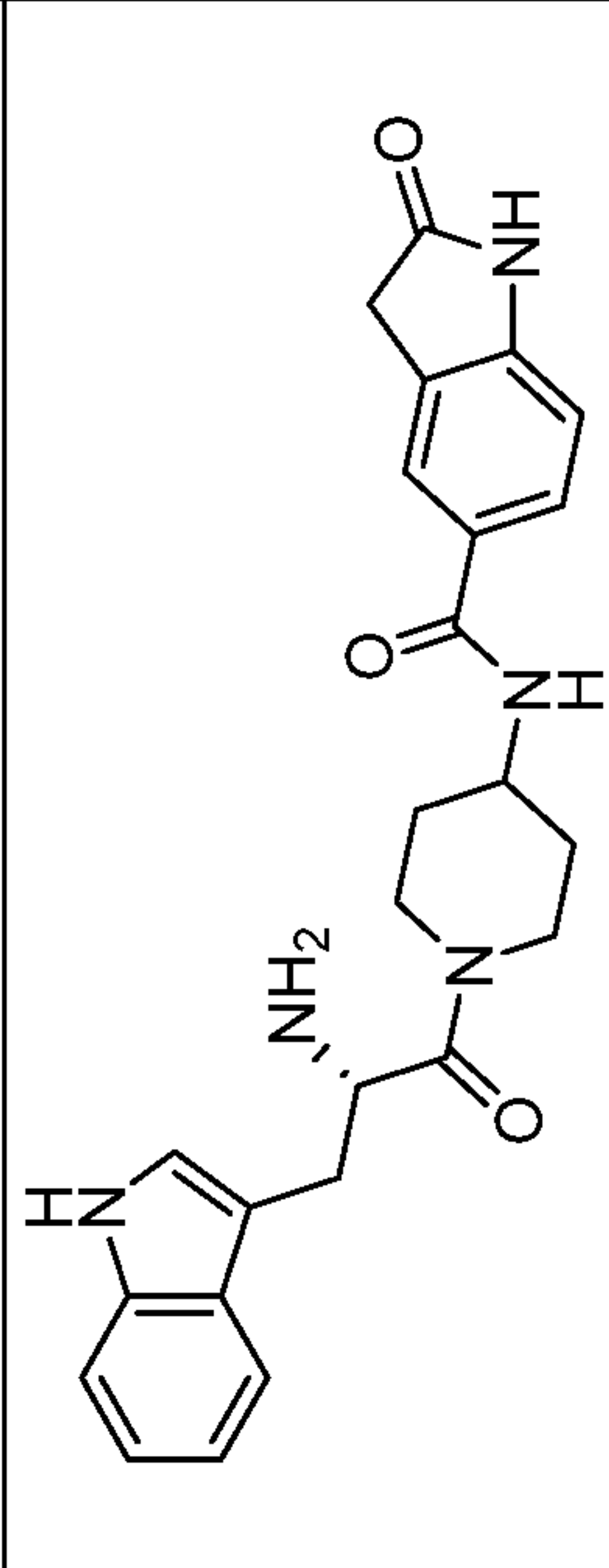
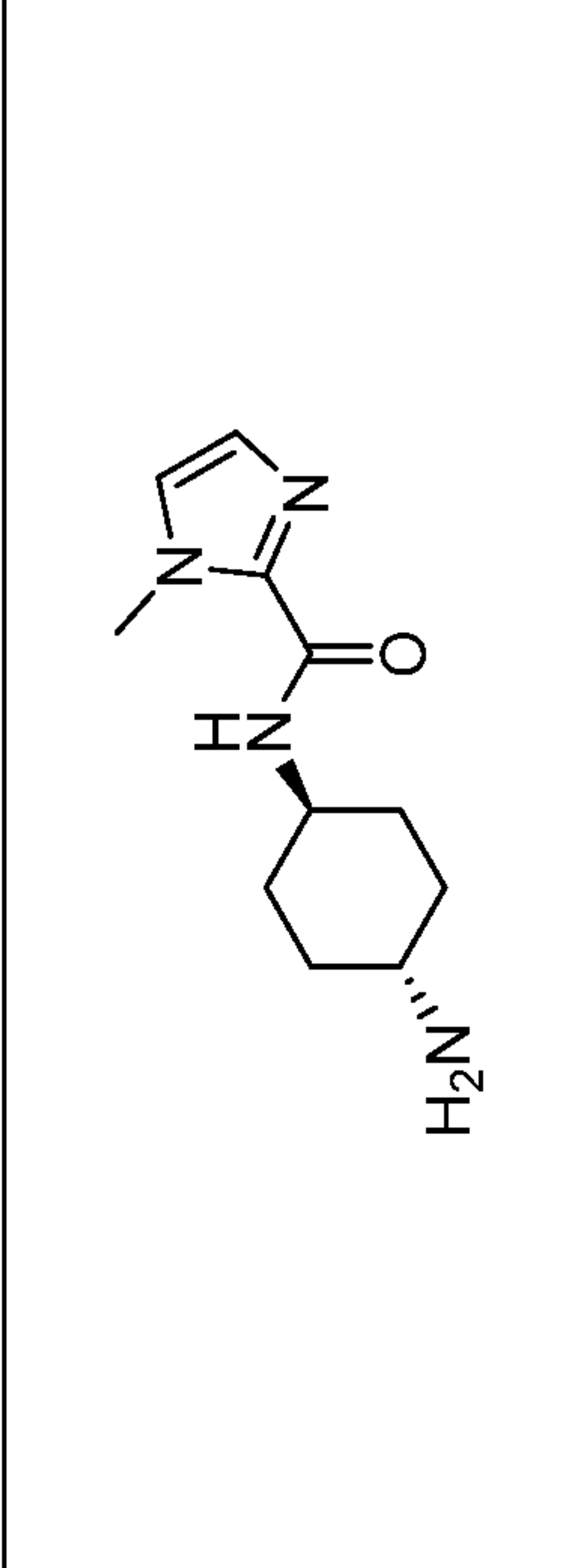
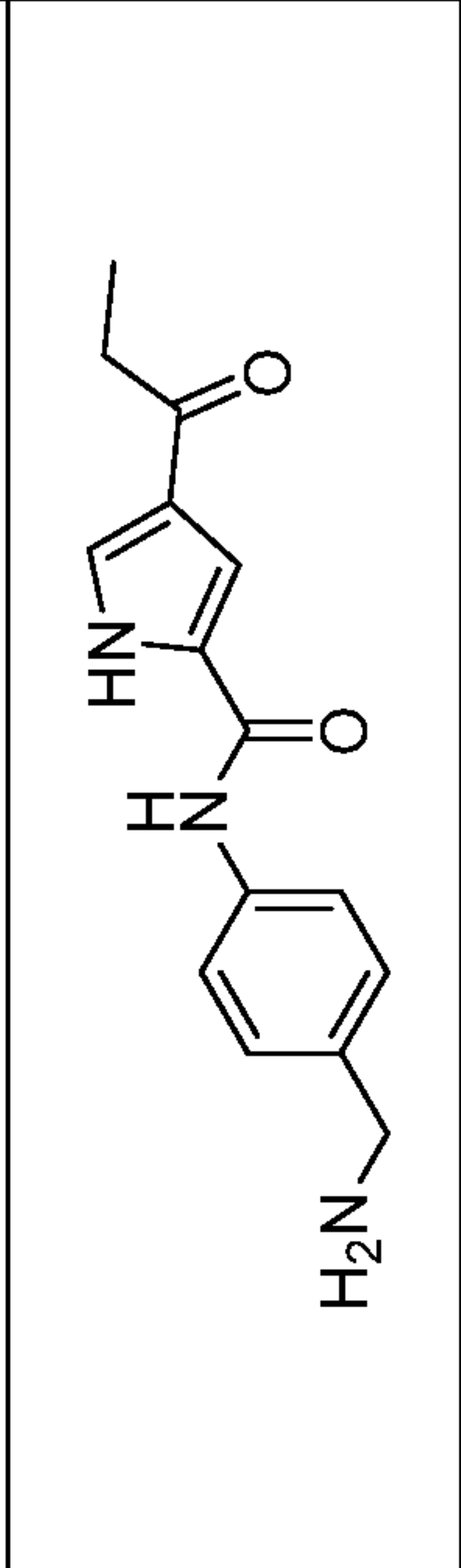
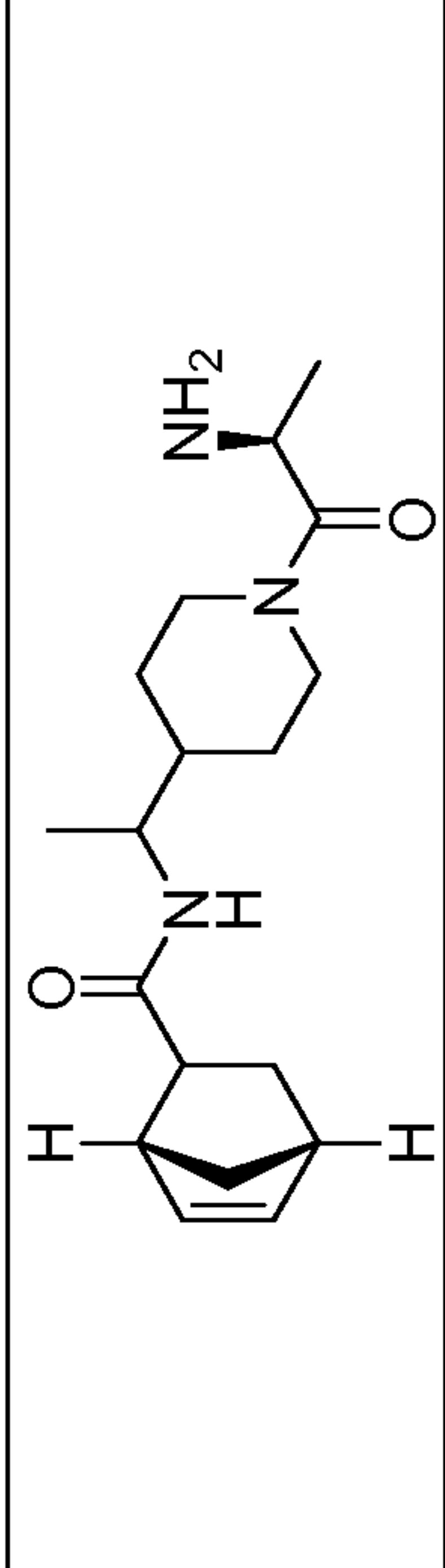
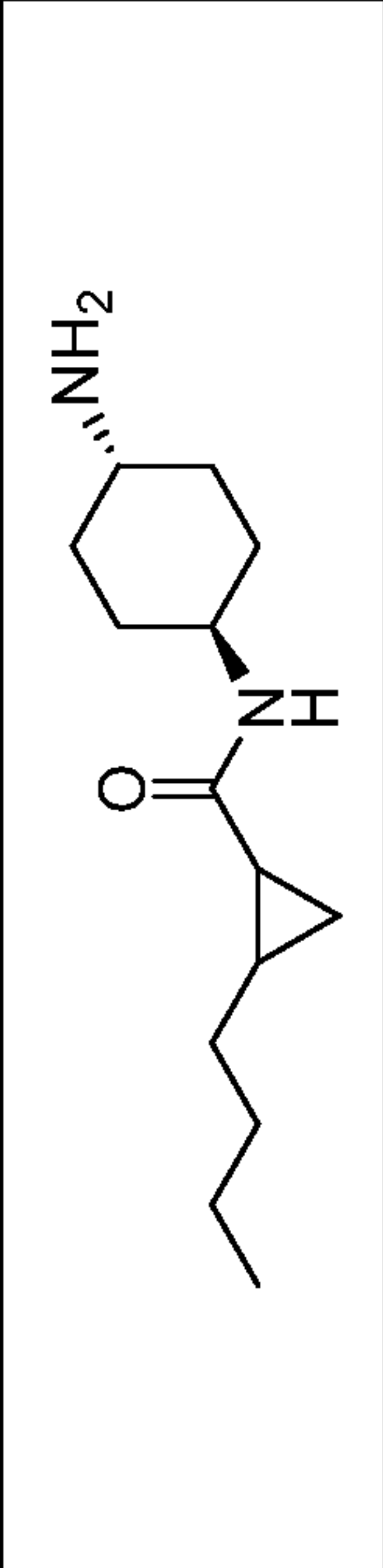
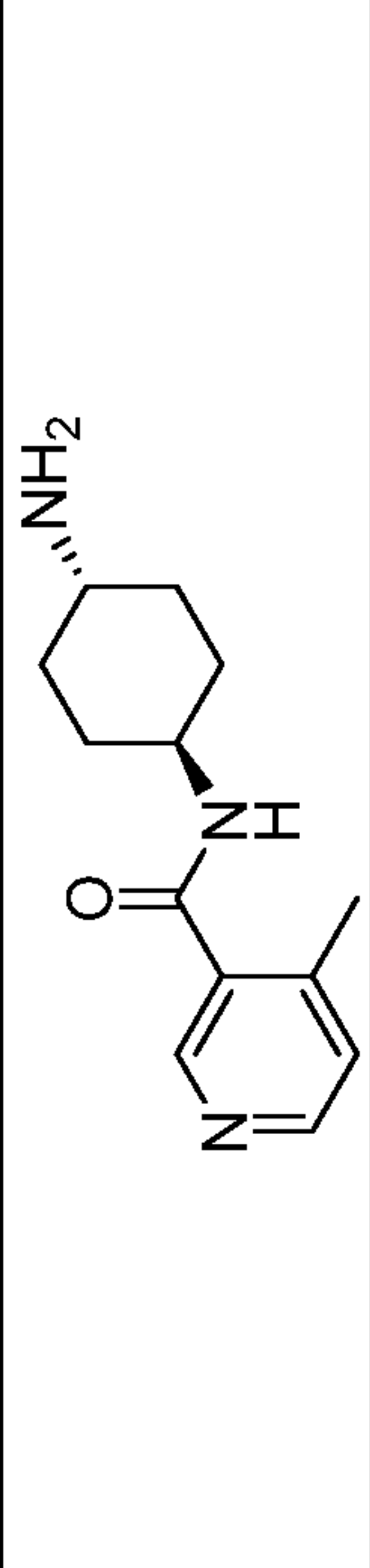
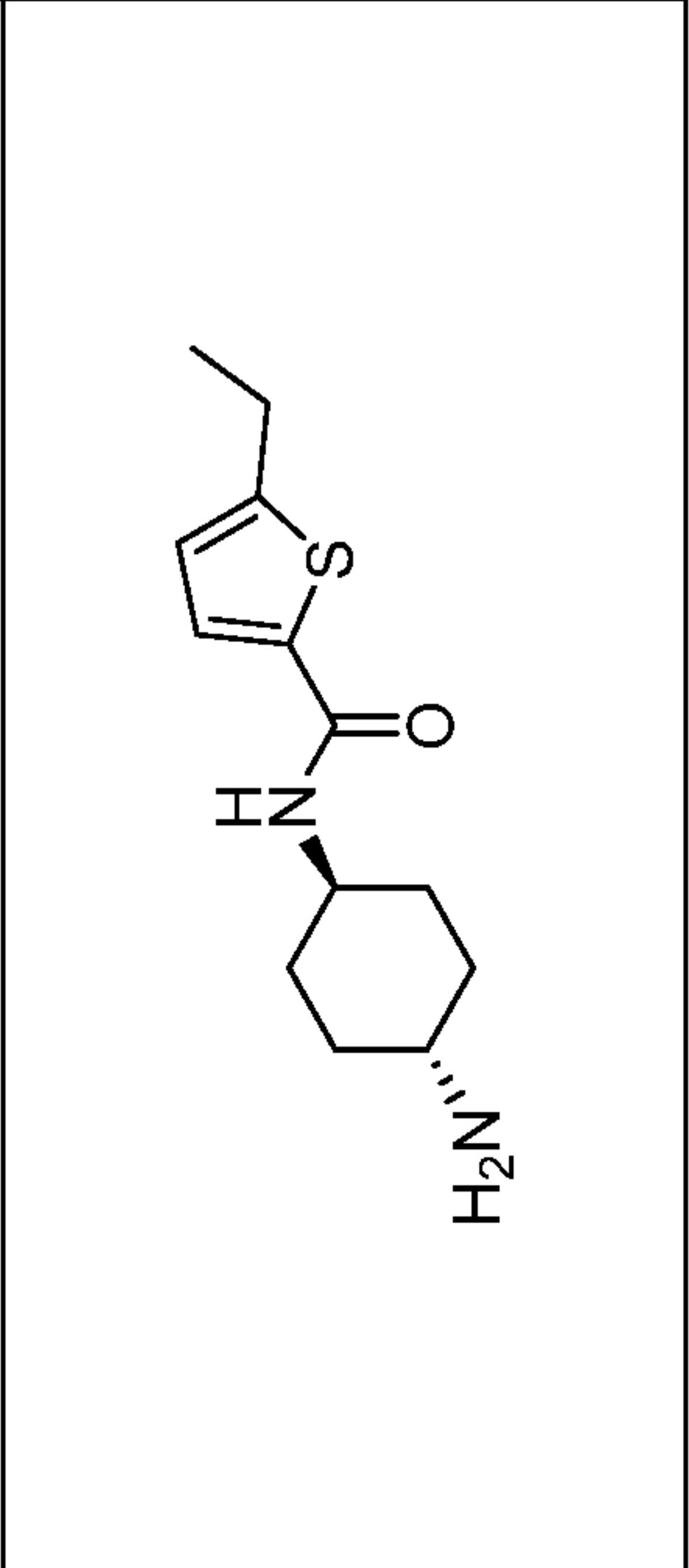
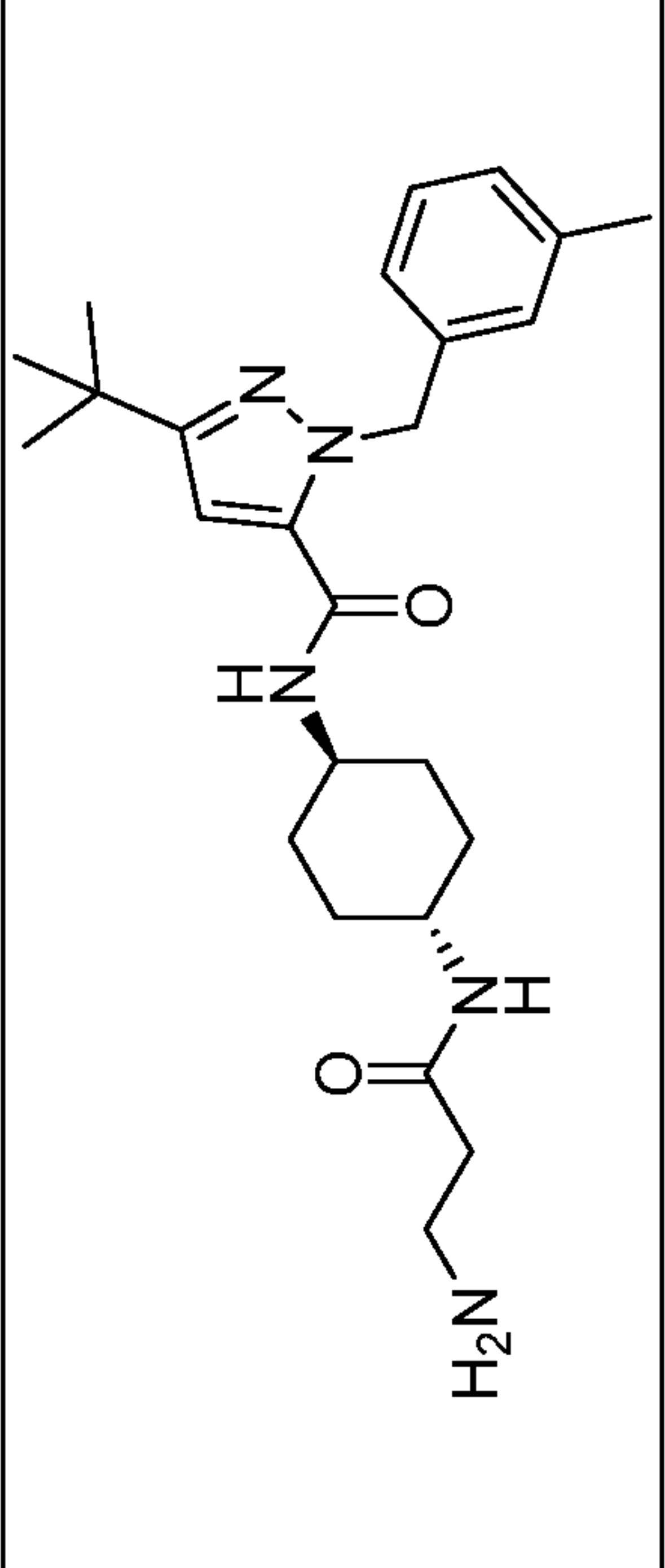
28		HCl	315		TFA
29		HCl	316		TFA
30		HCl	317		HCl

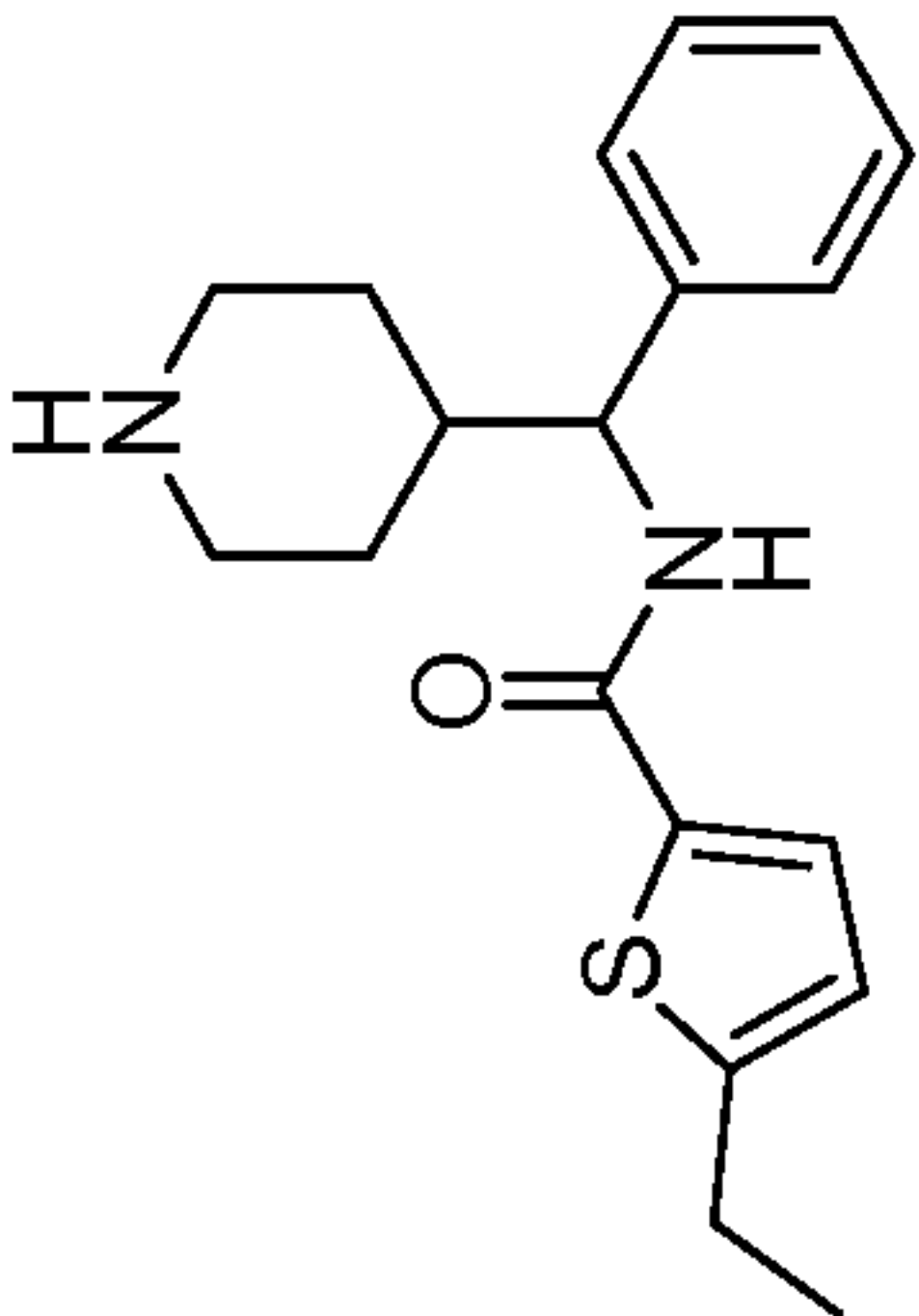
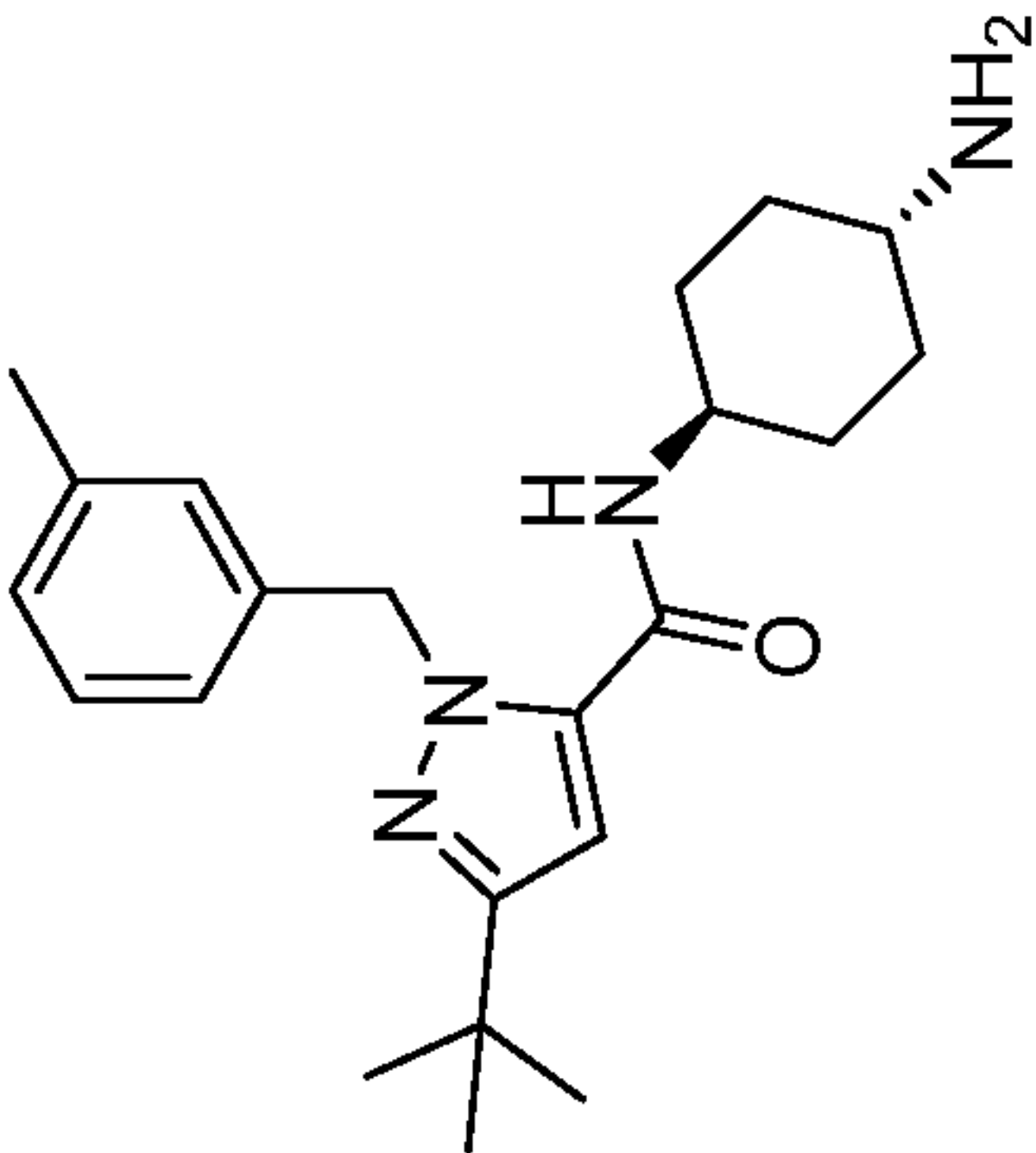
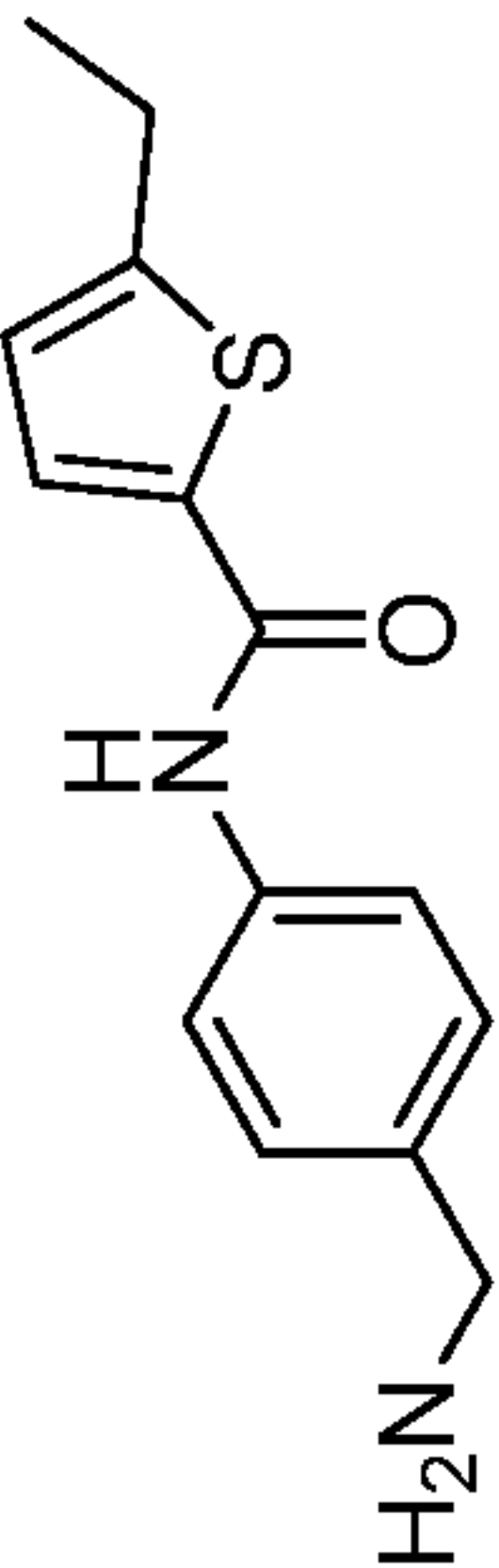
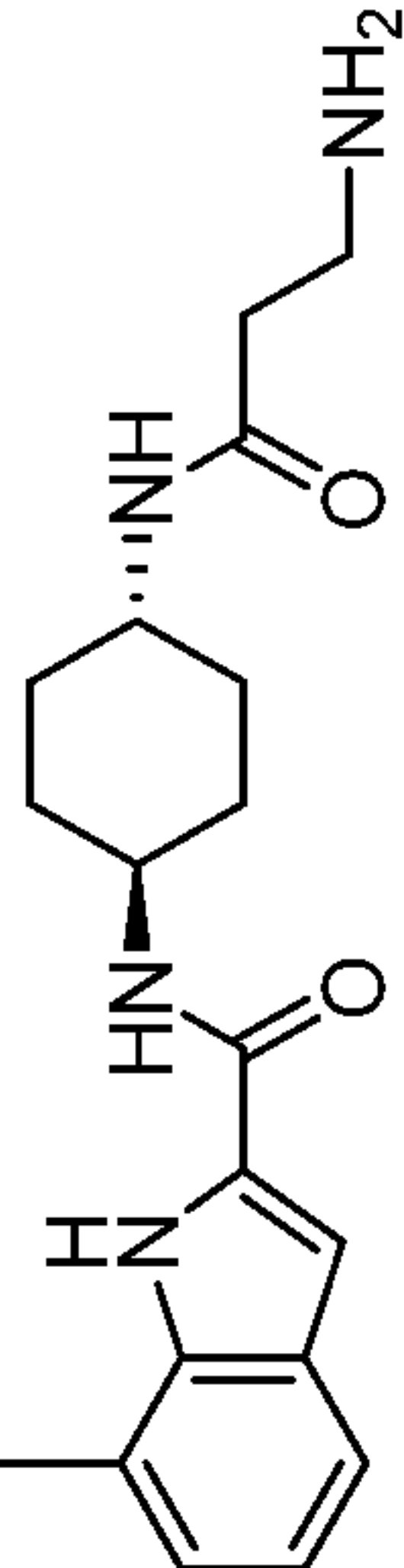
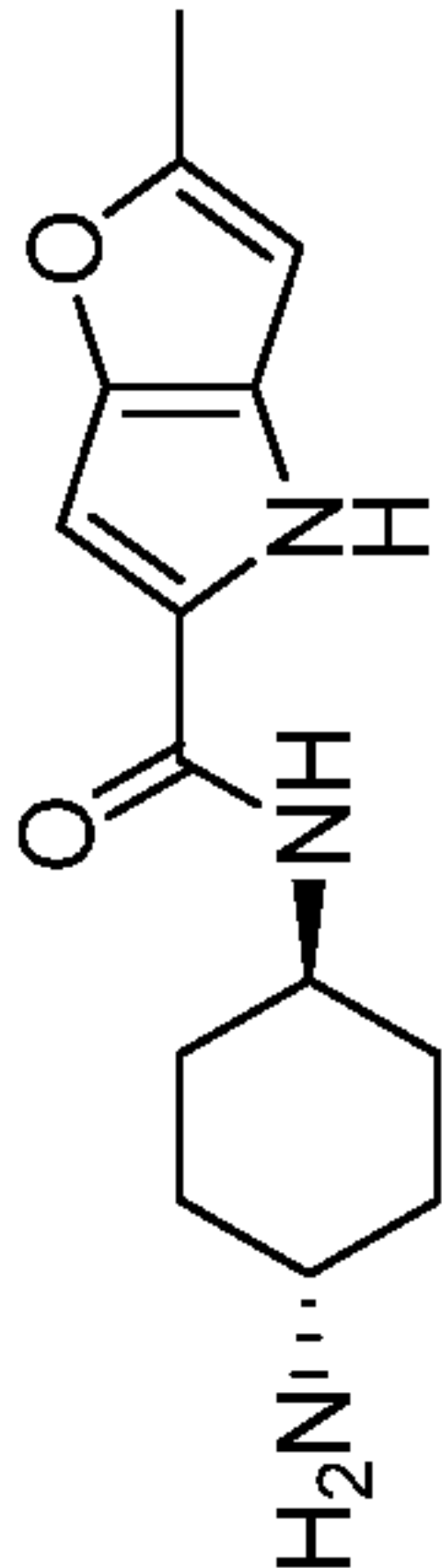
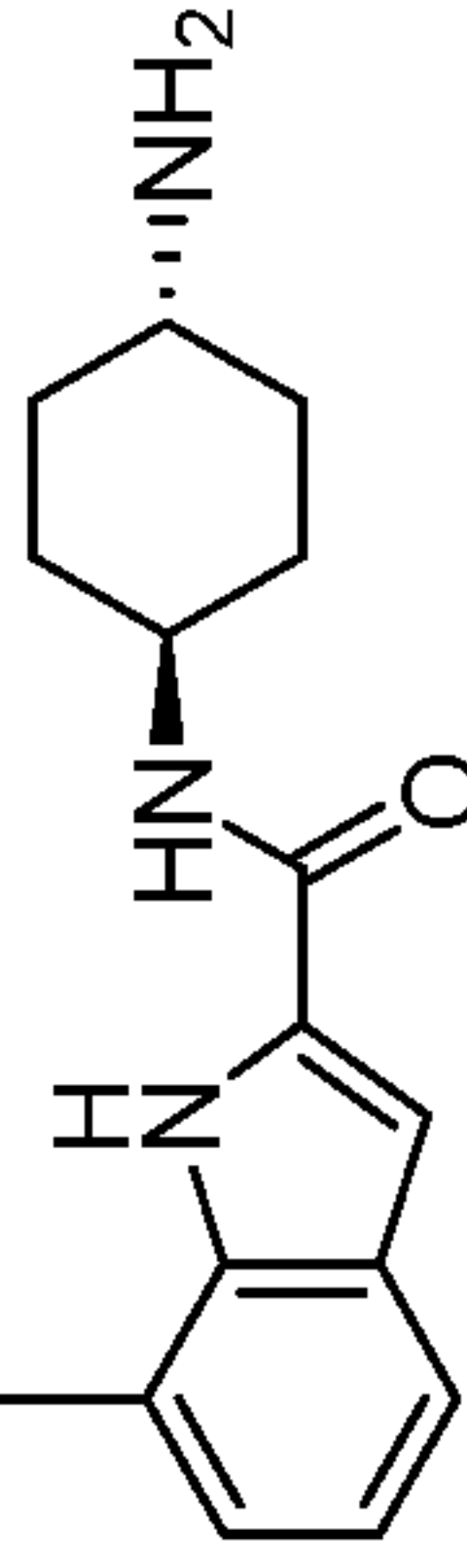
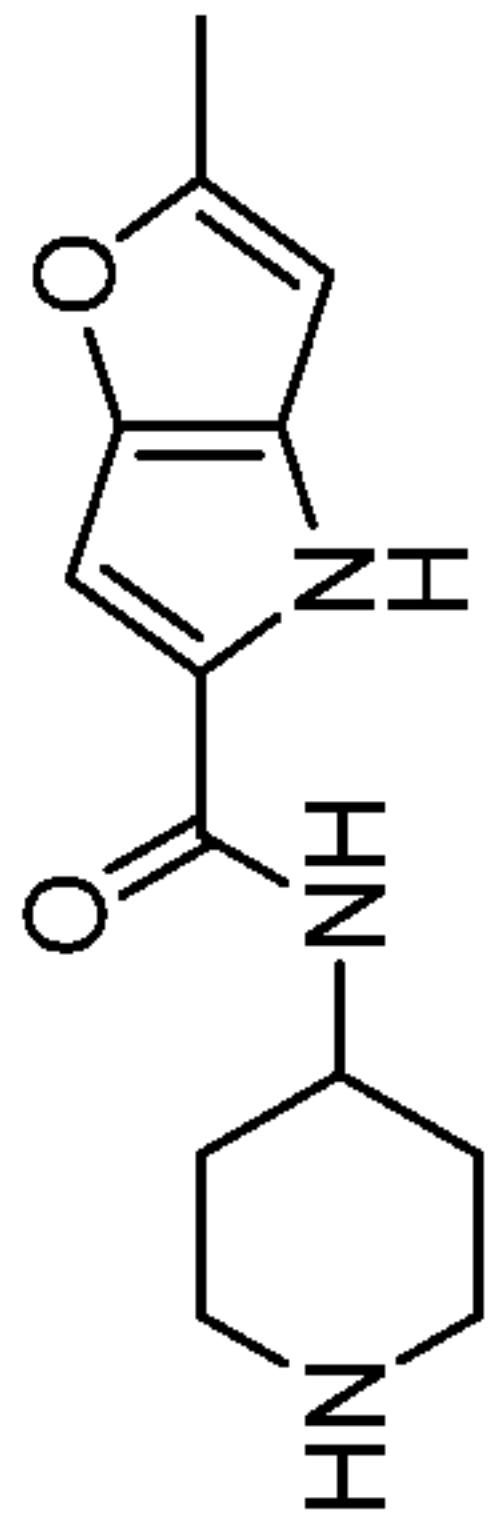
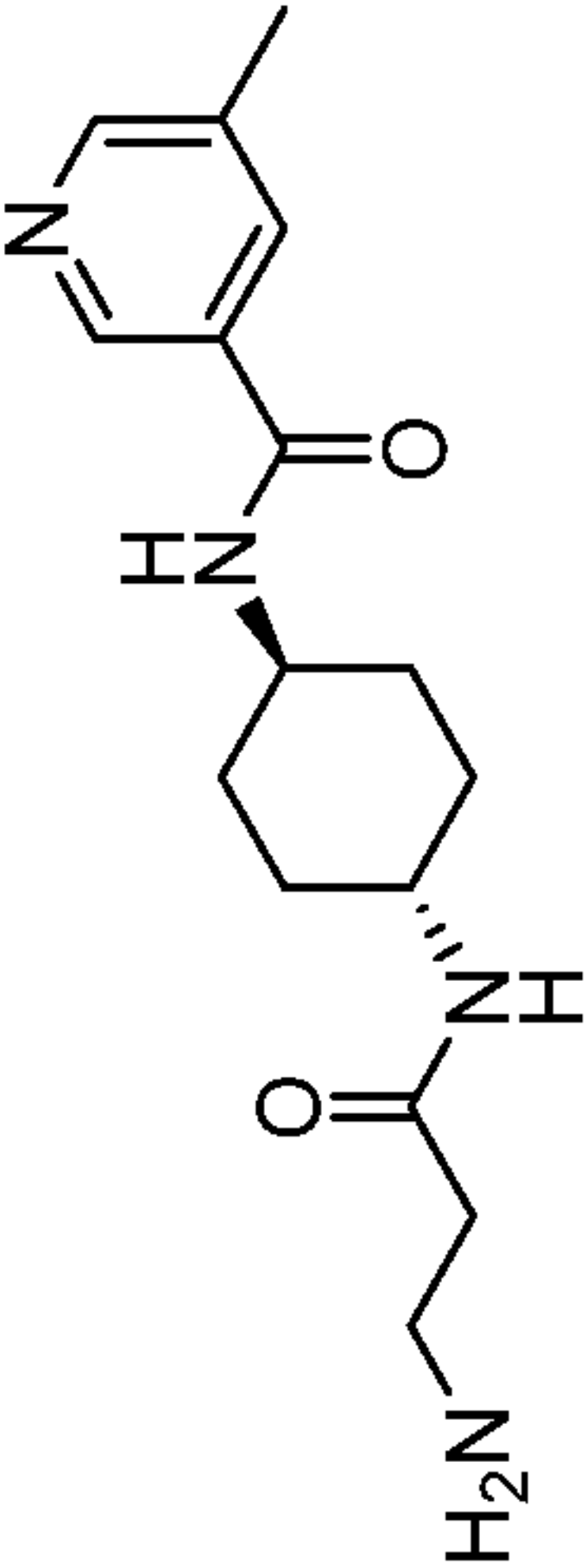
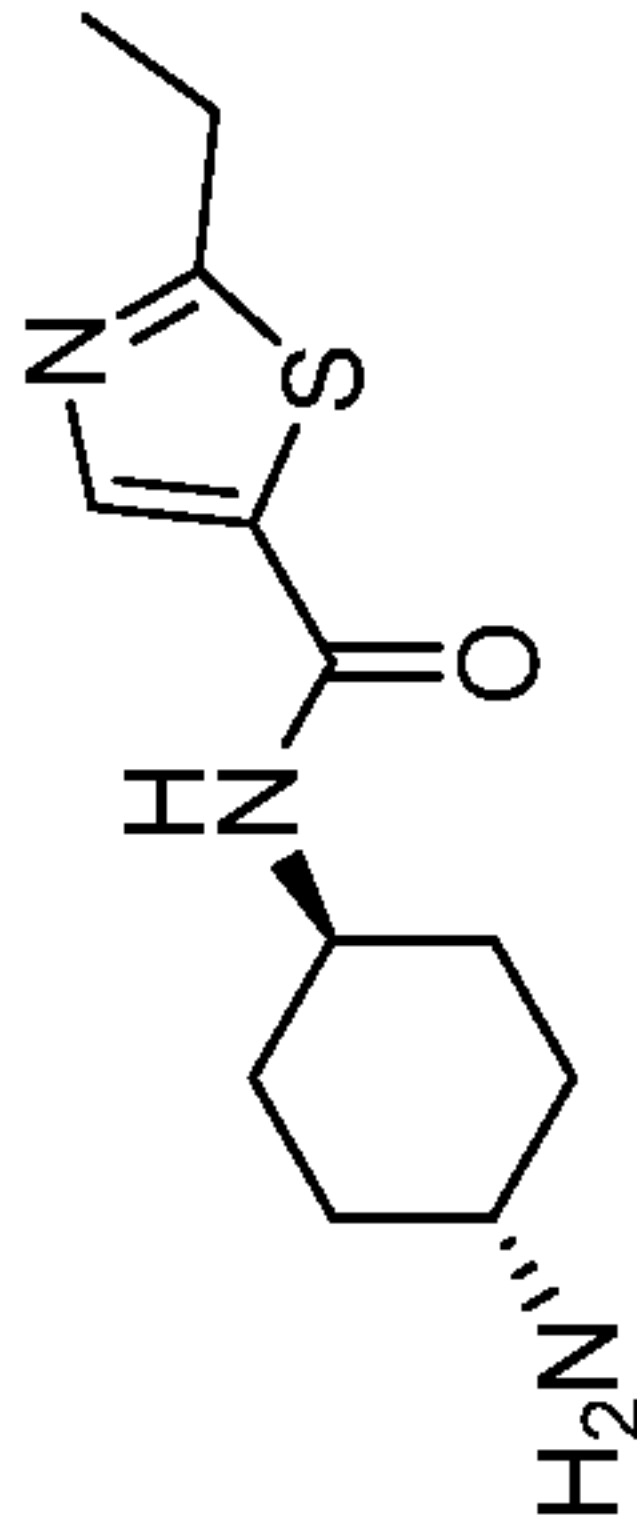
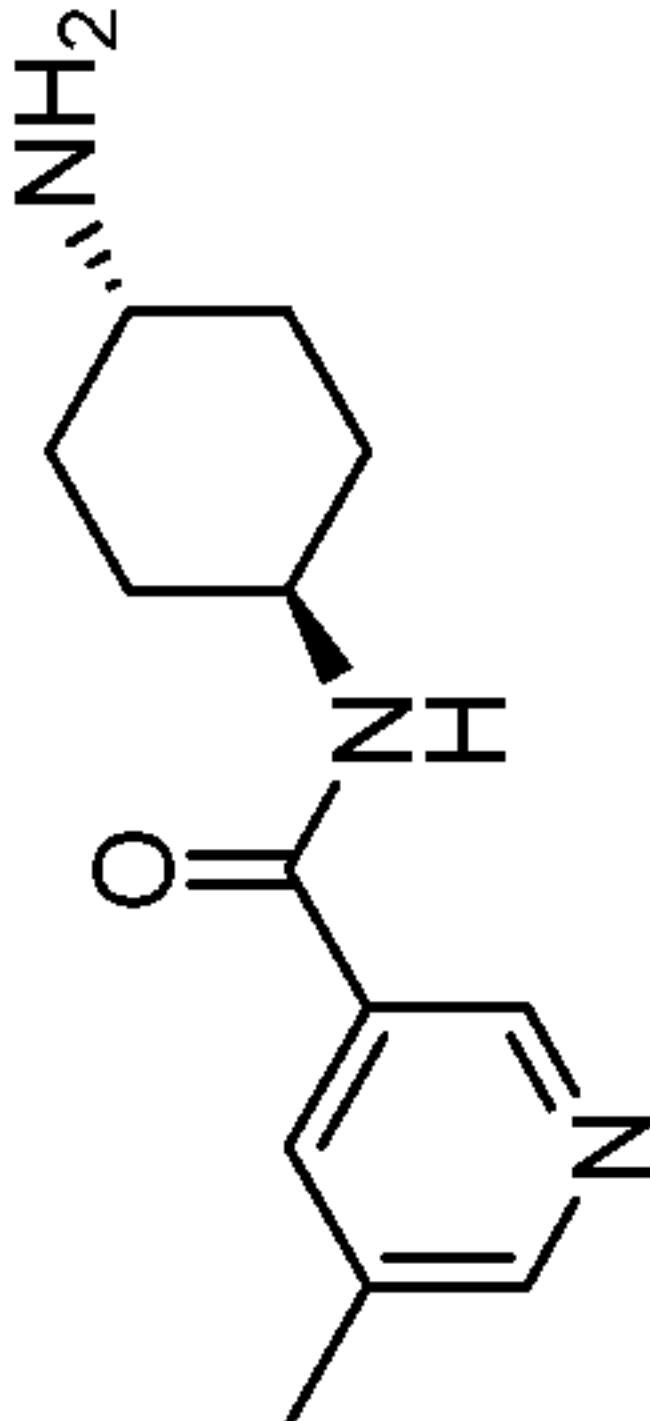
31		HCl	318		HCl
32		HCl	319		TFA
33		HCl	320		None
34		HCl	321		HCl

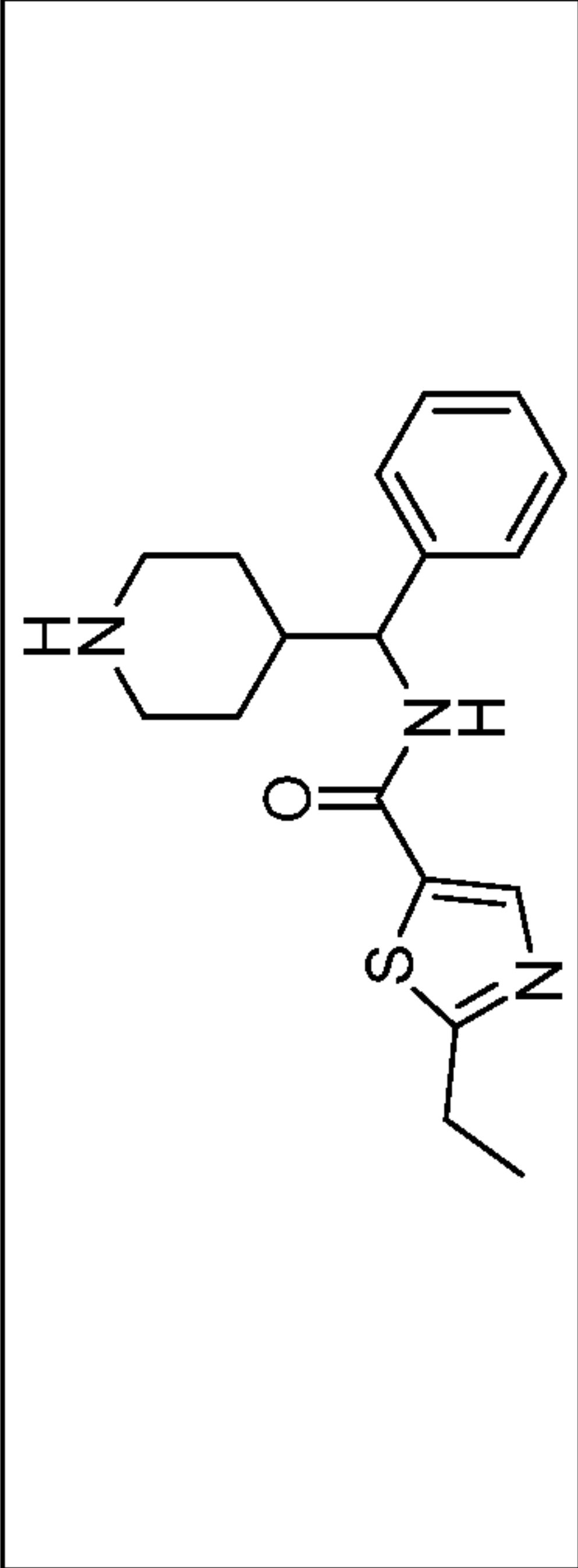
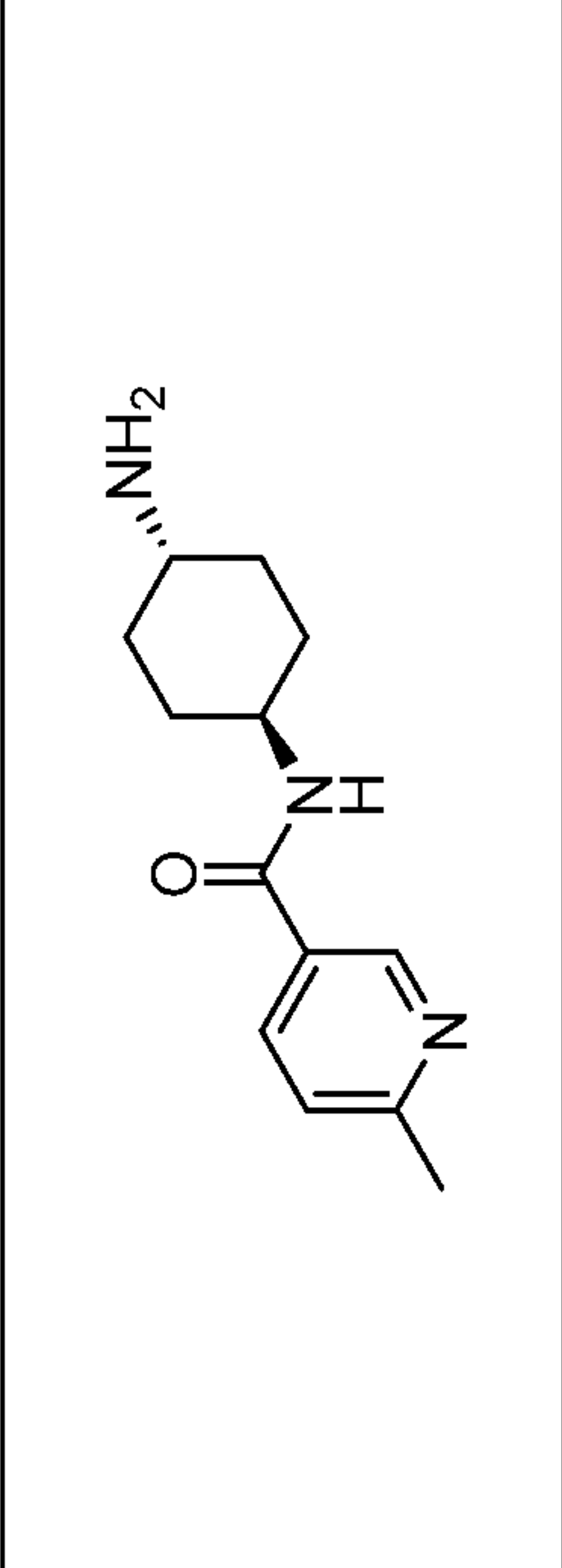
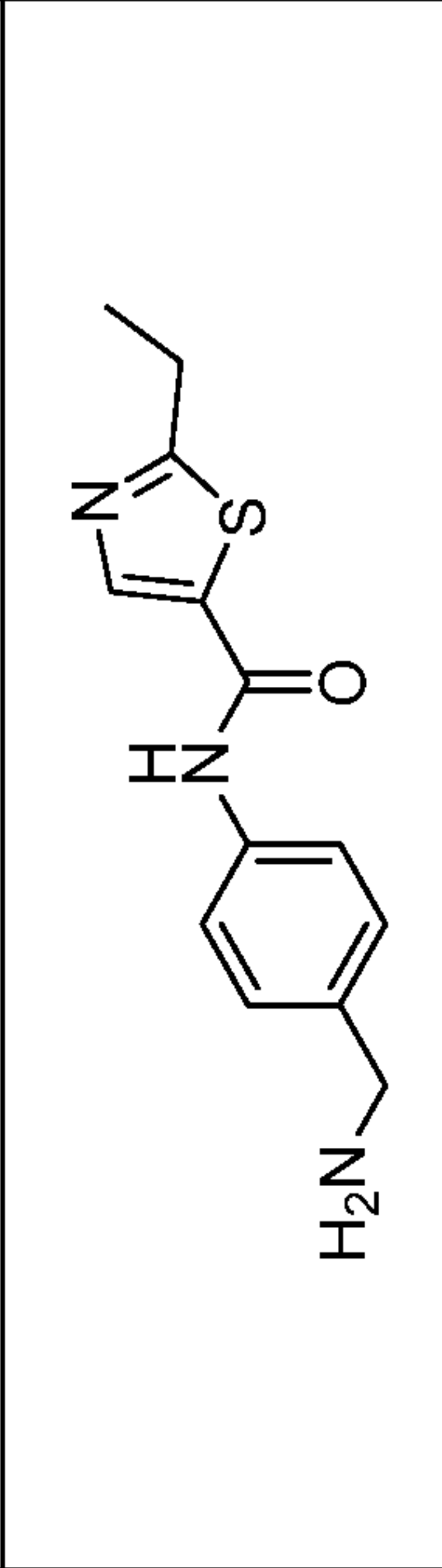
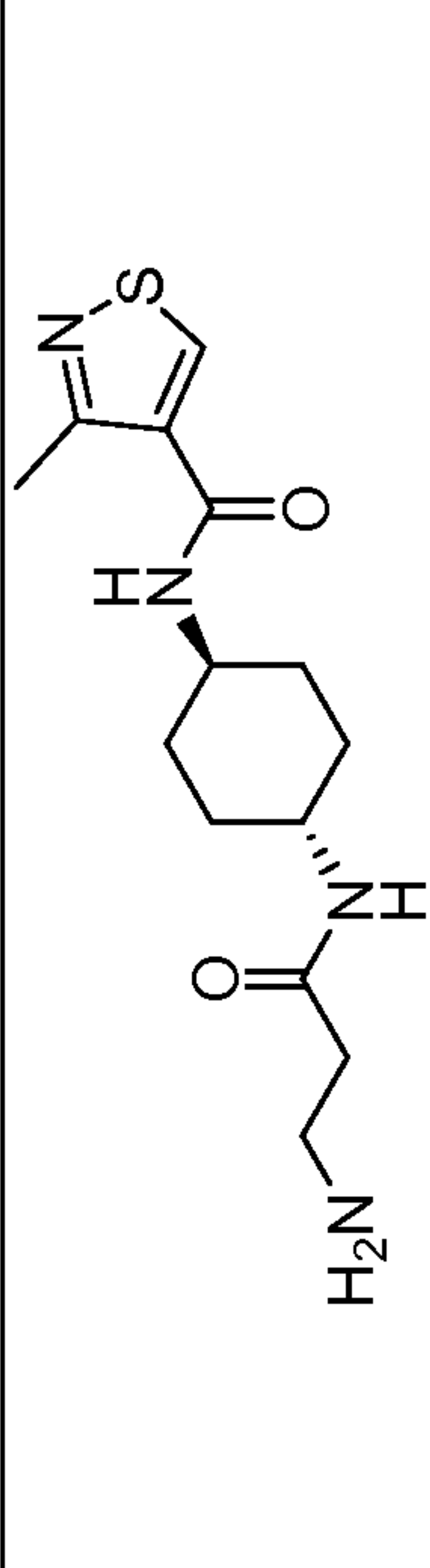
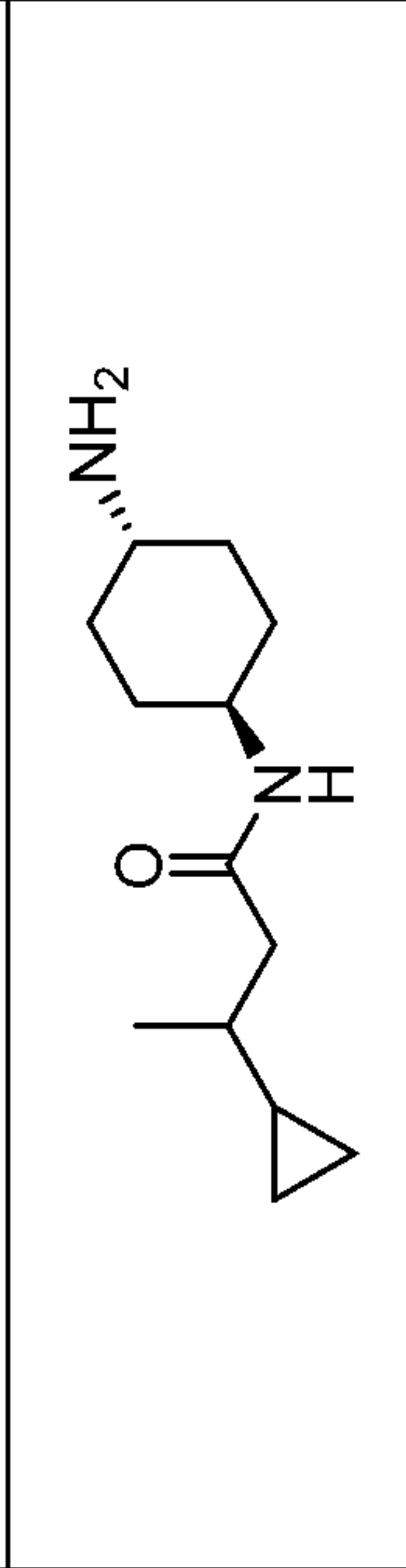
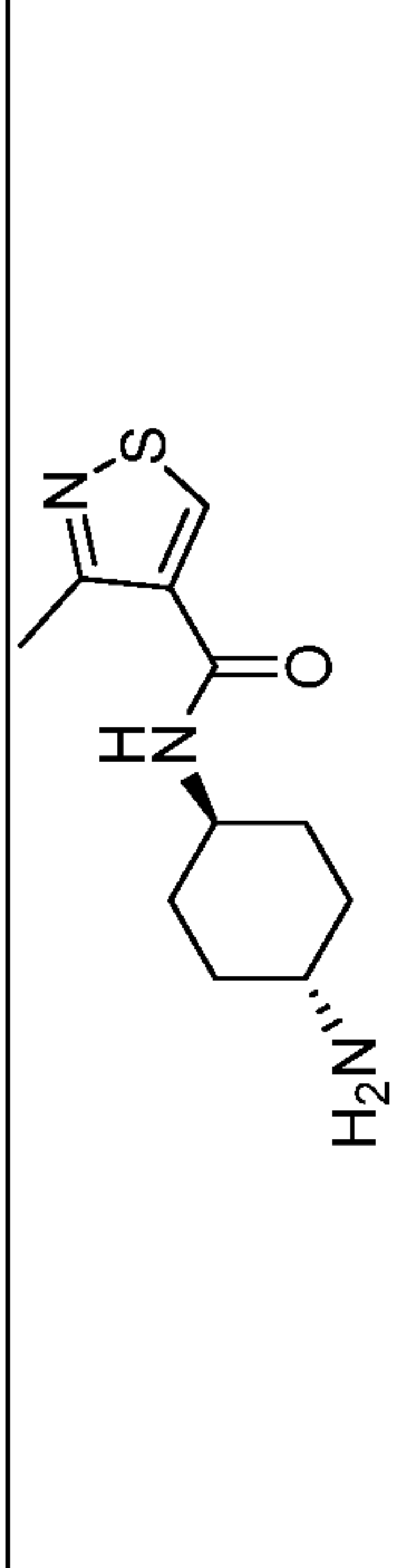
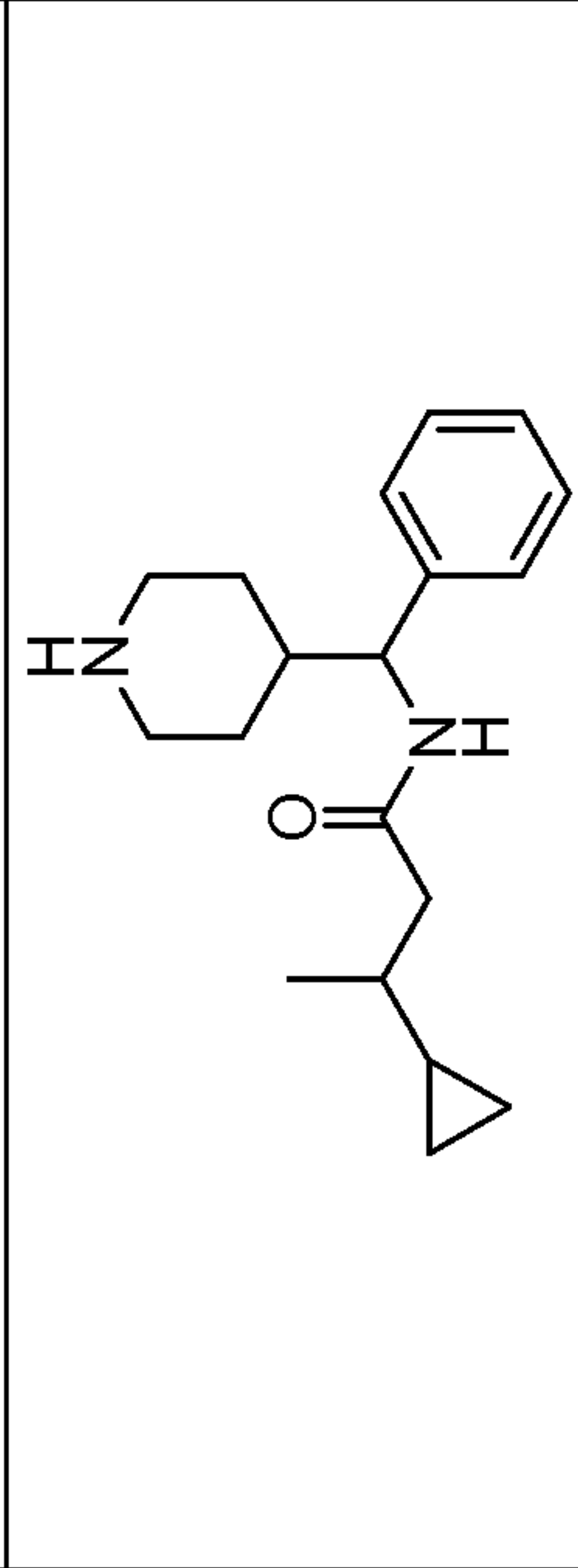
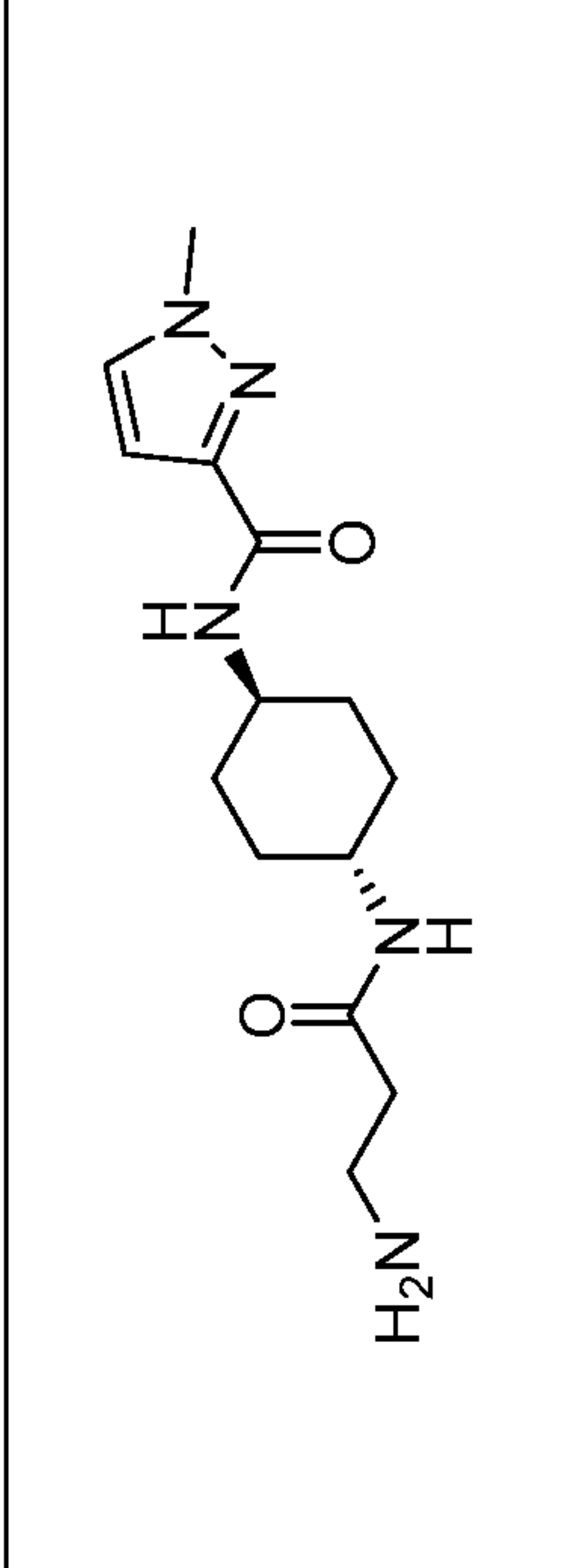
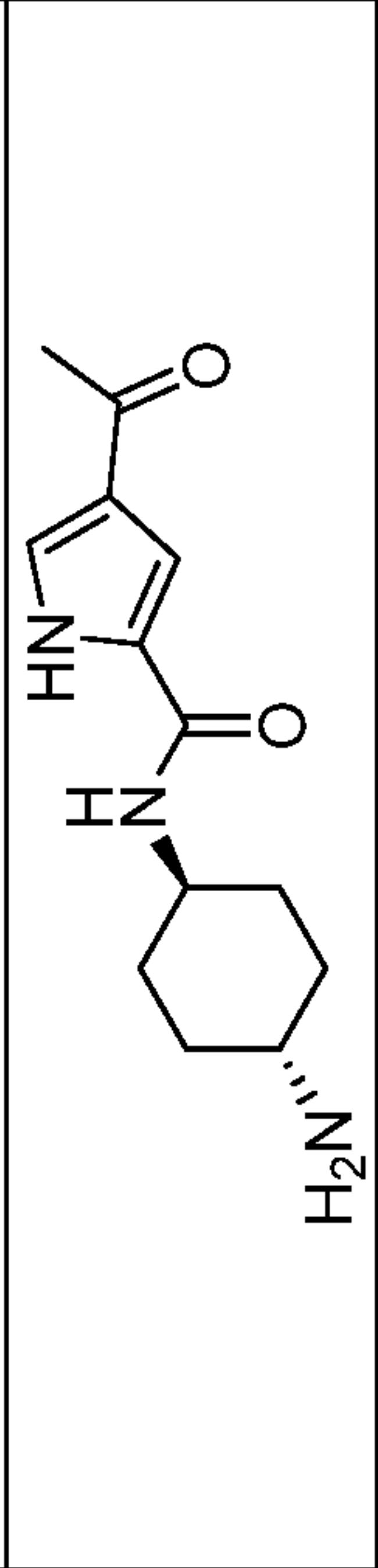
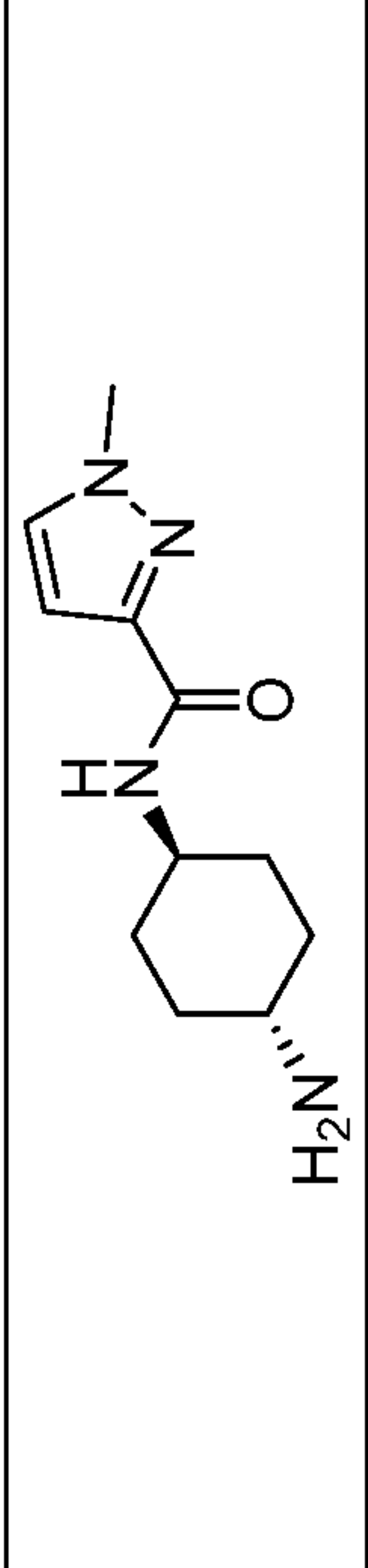
35		HCl	322		None
36		HCl	323		TFA
37		HCl	324		TFA
38		None	325		HCl
39		None	326		HCl

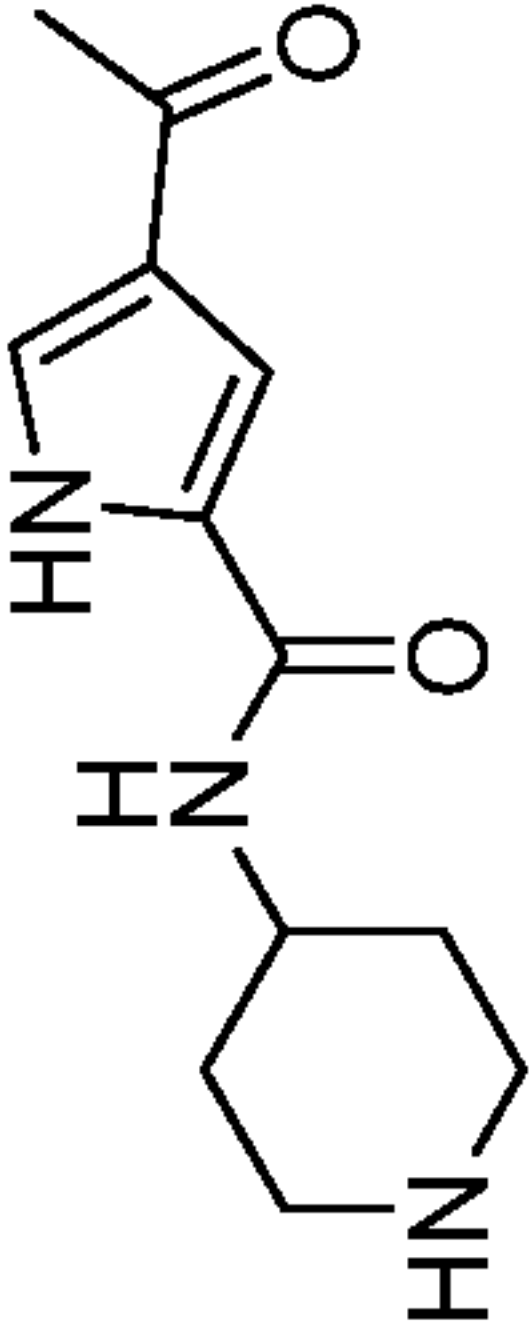
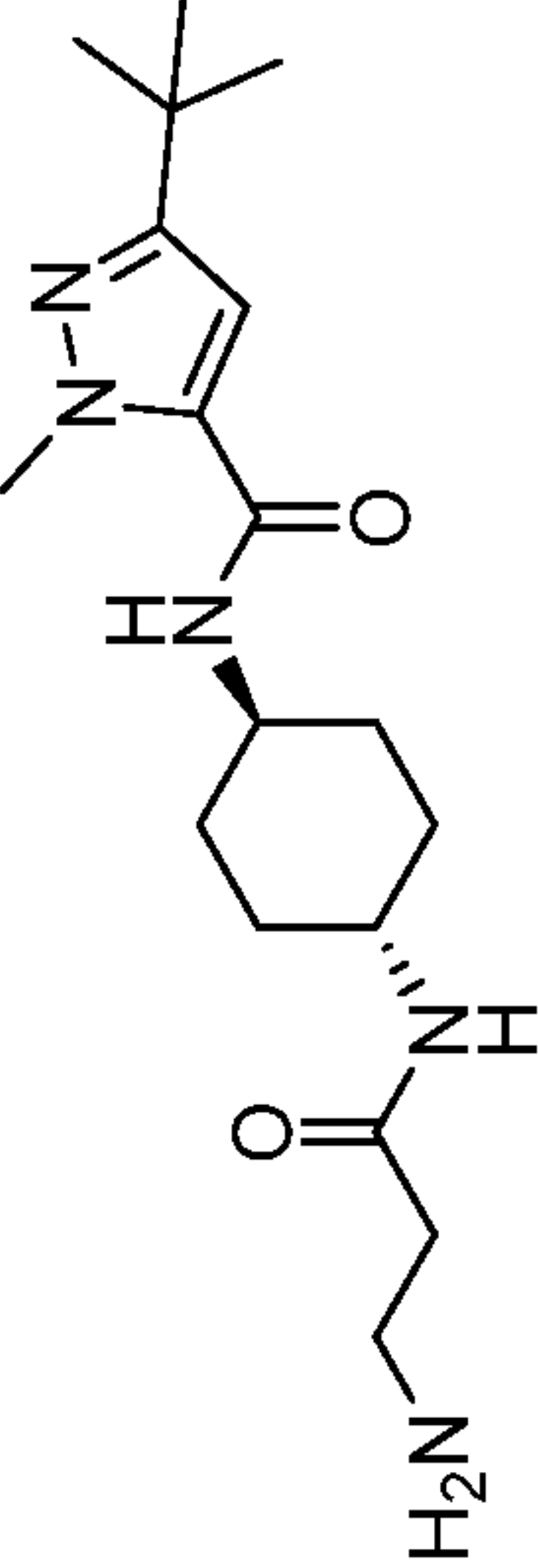
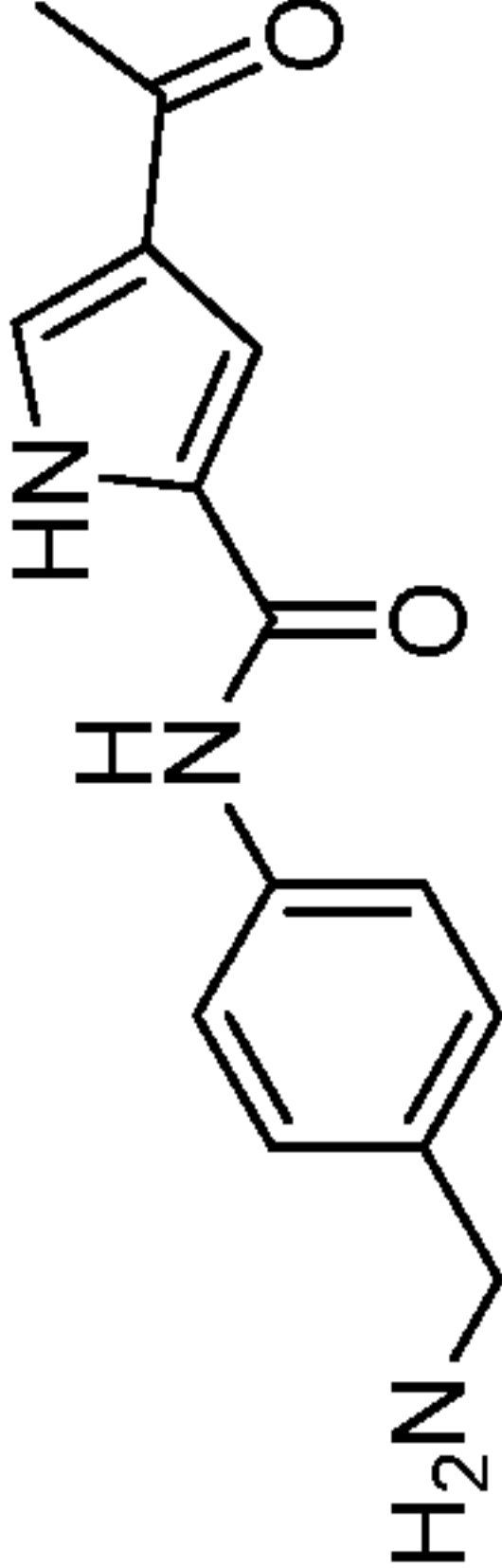
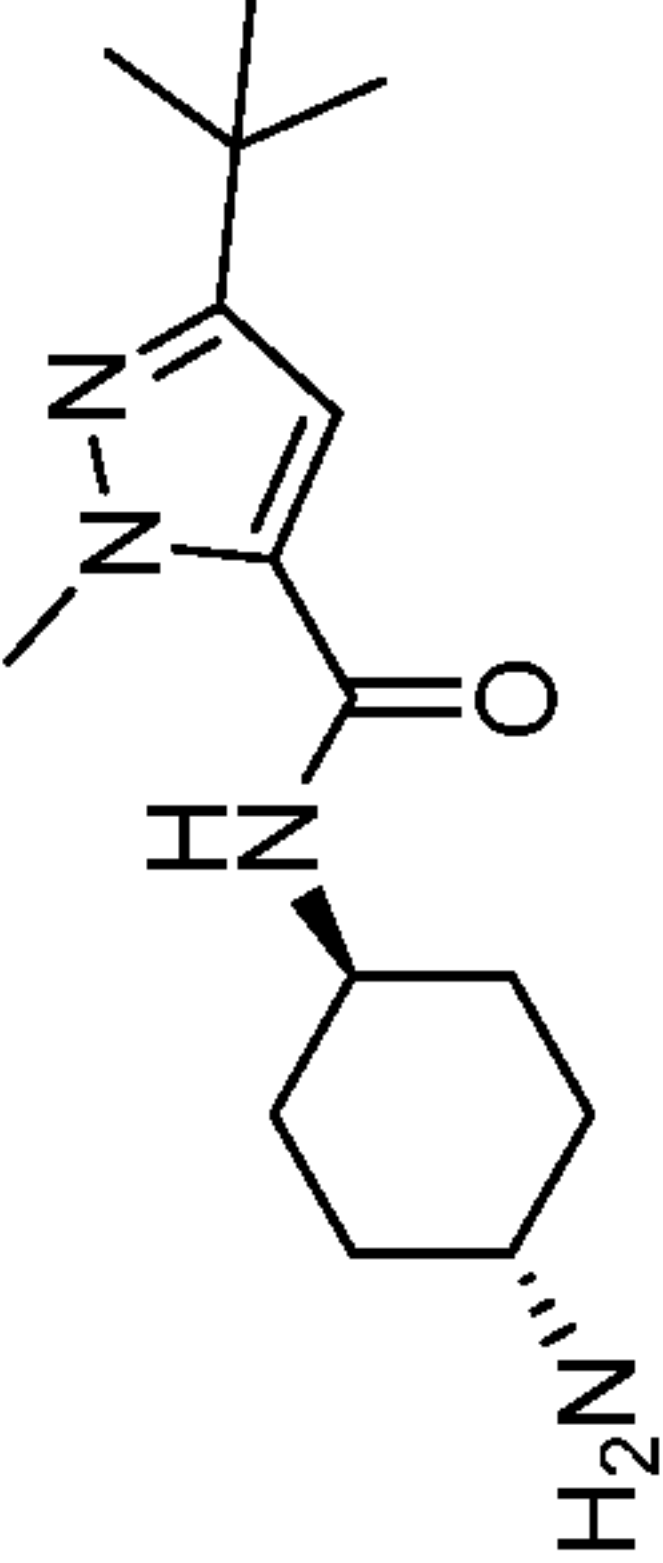
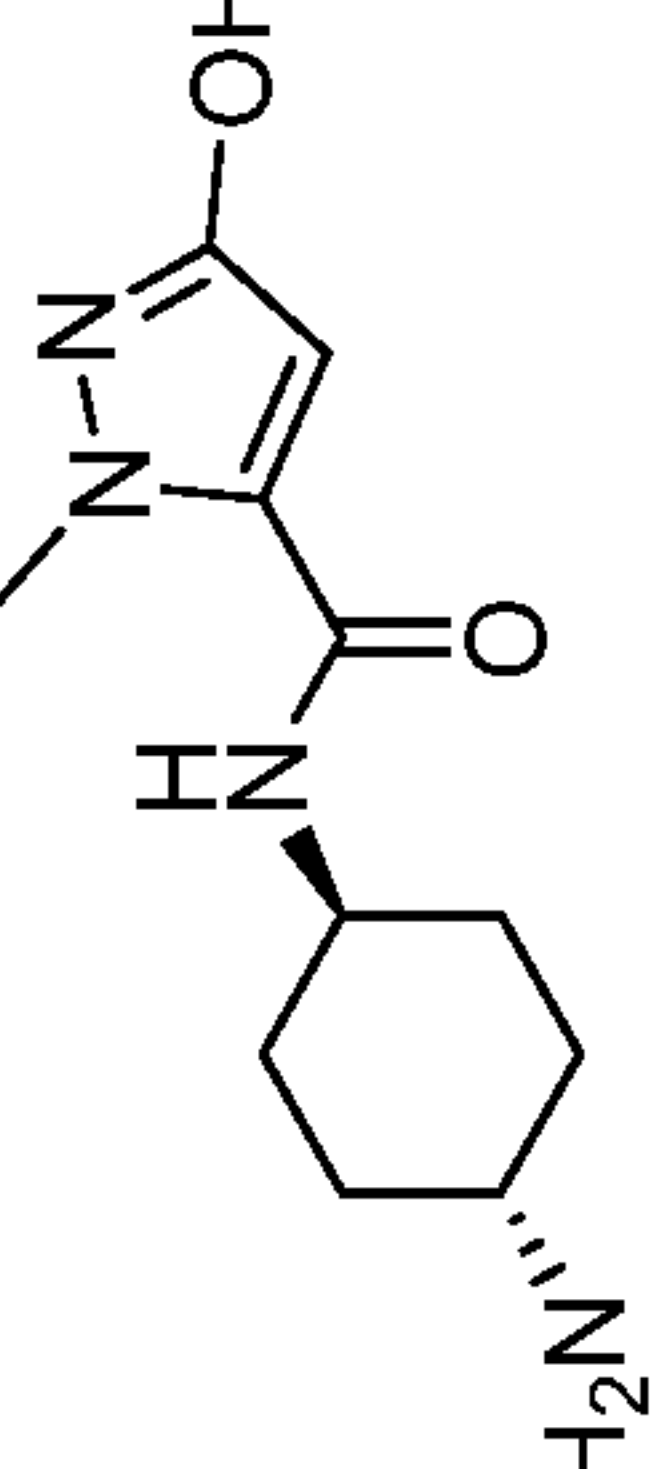
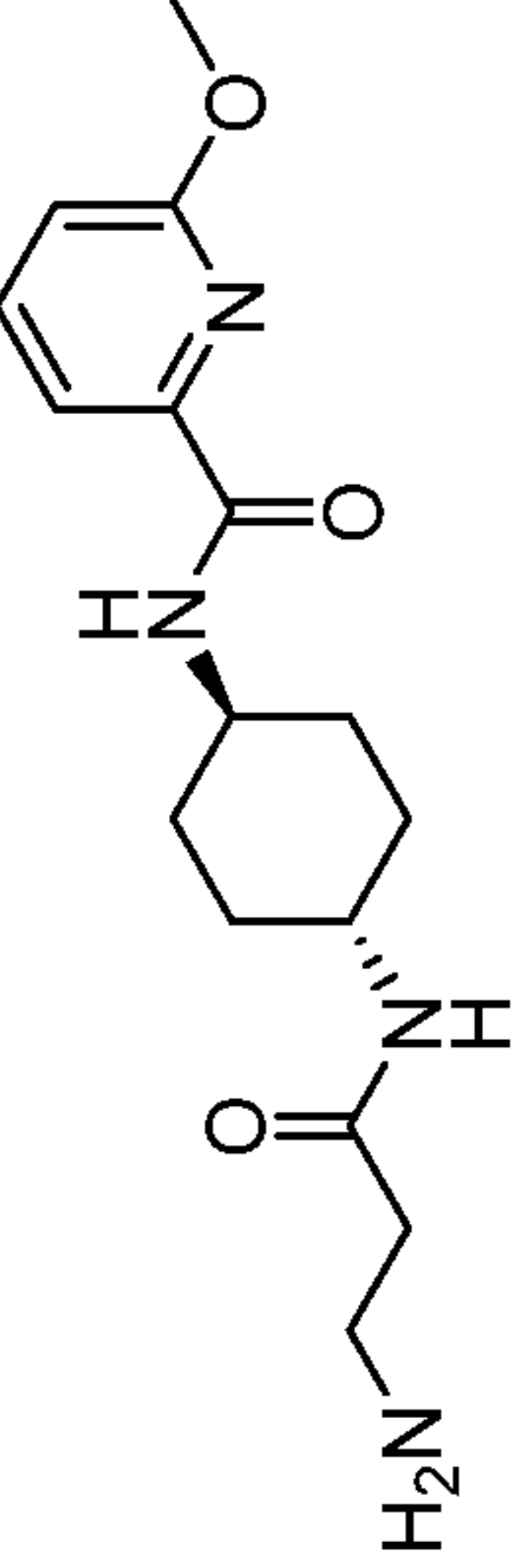
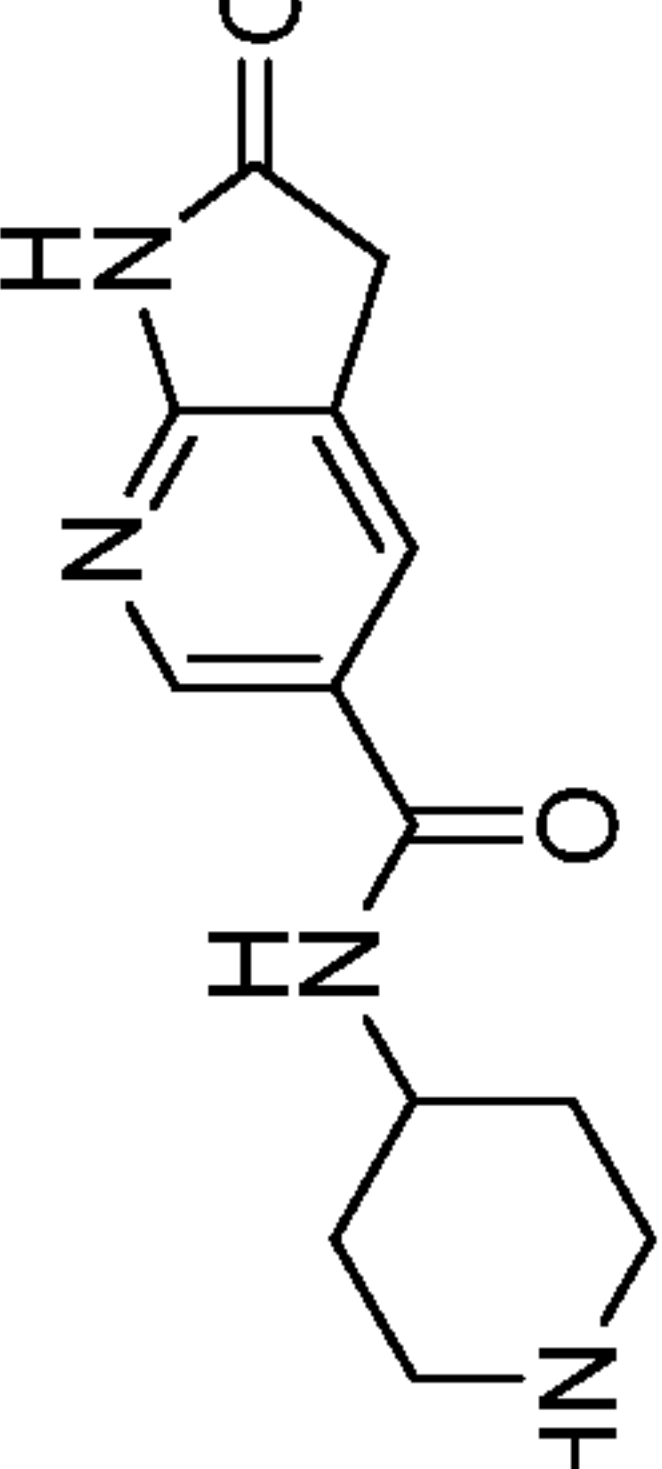
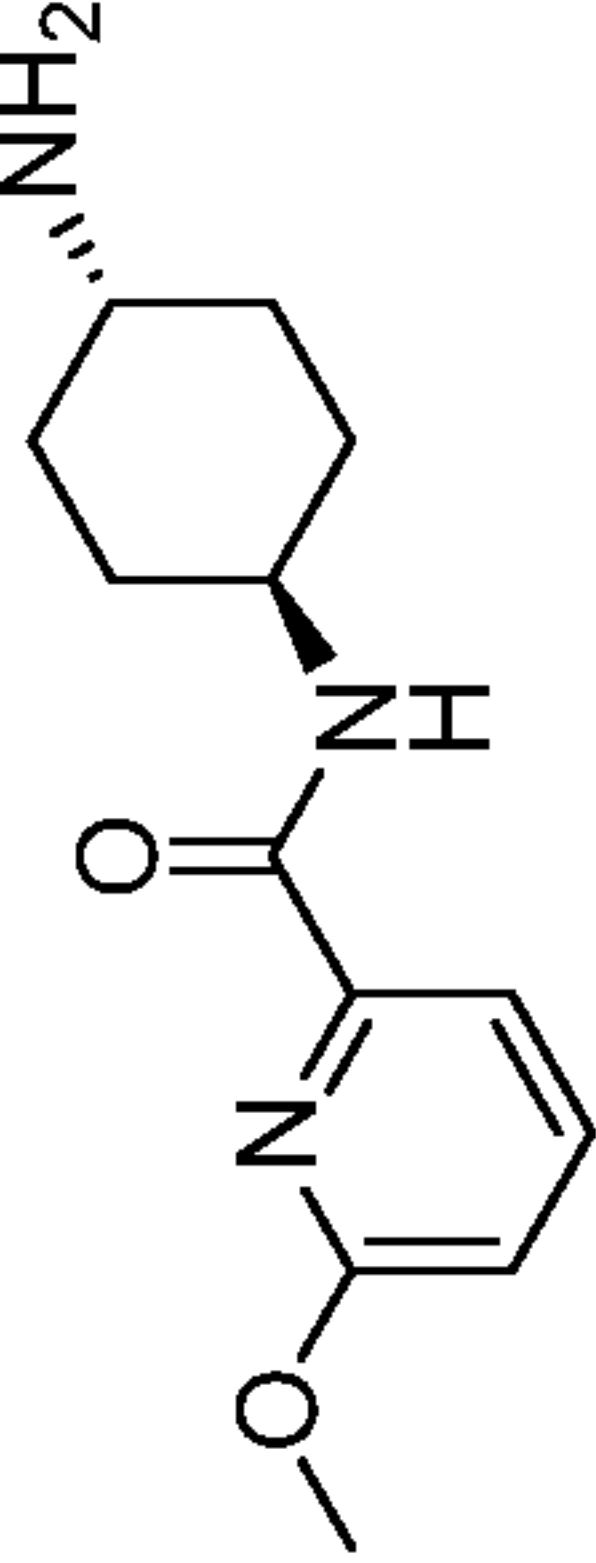
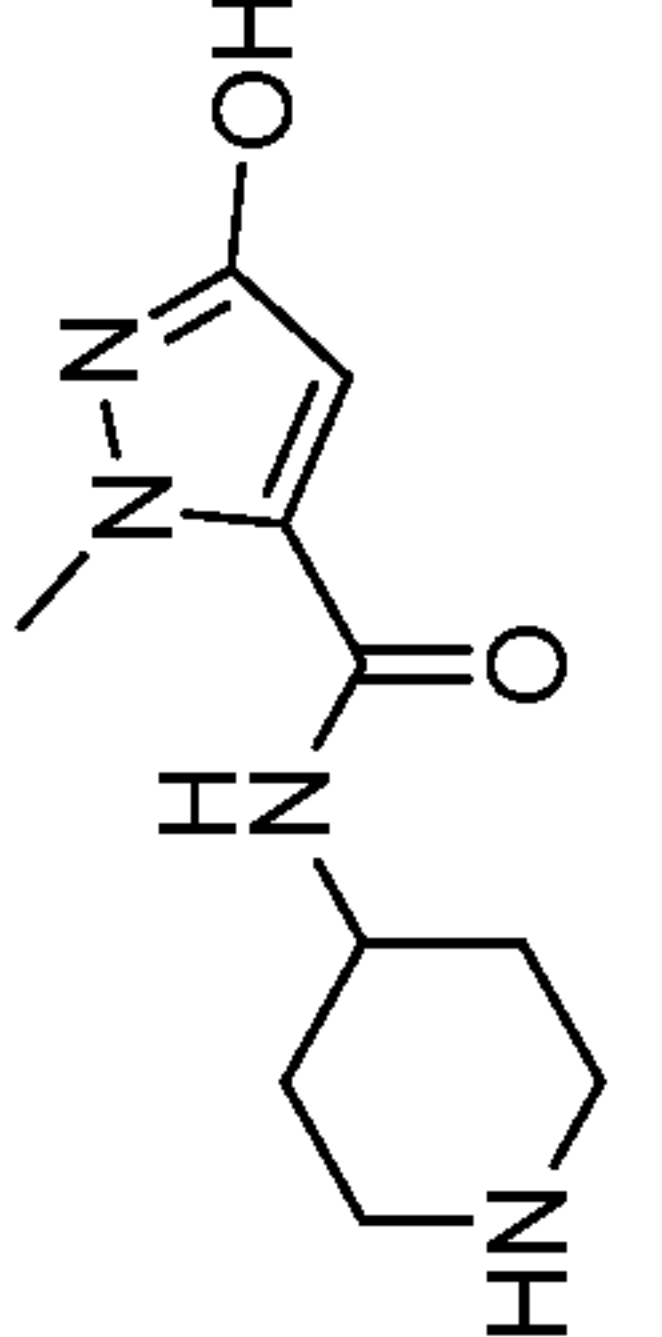
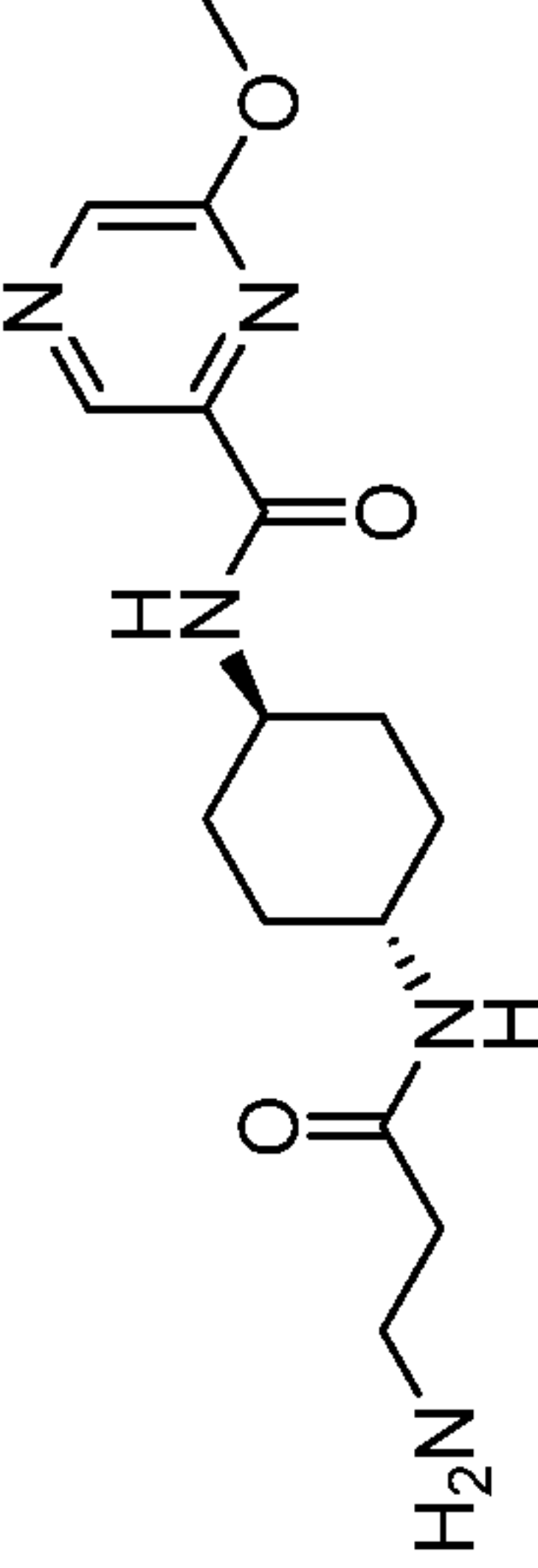
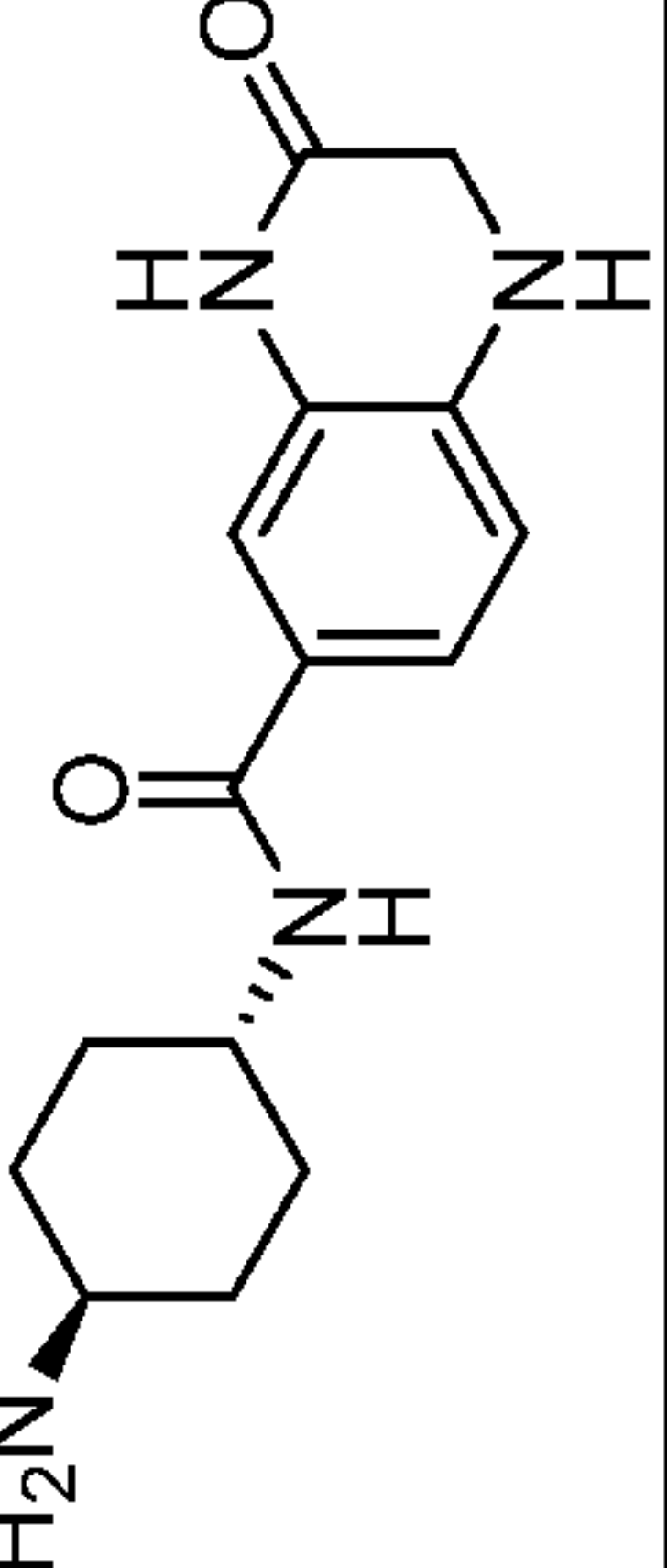
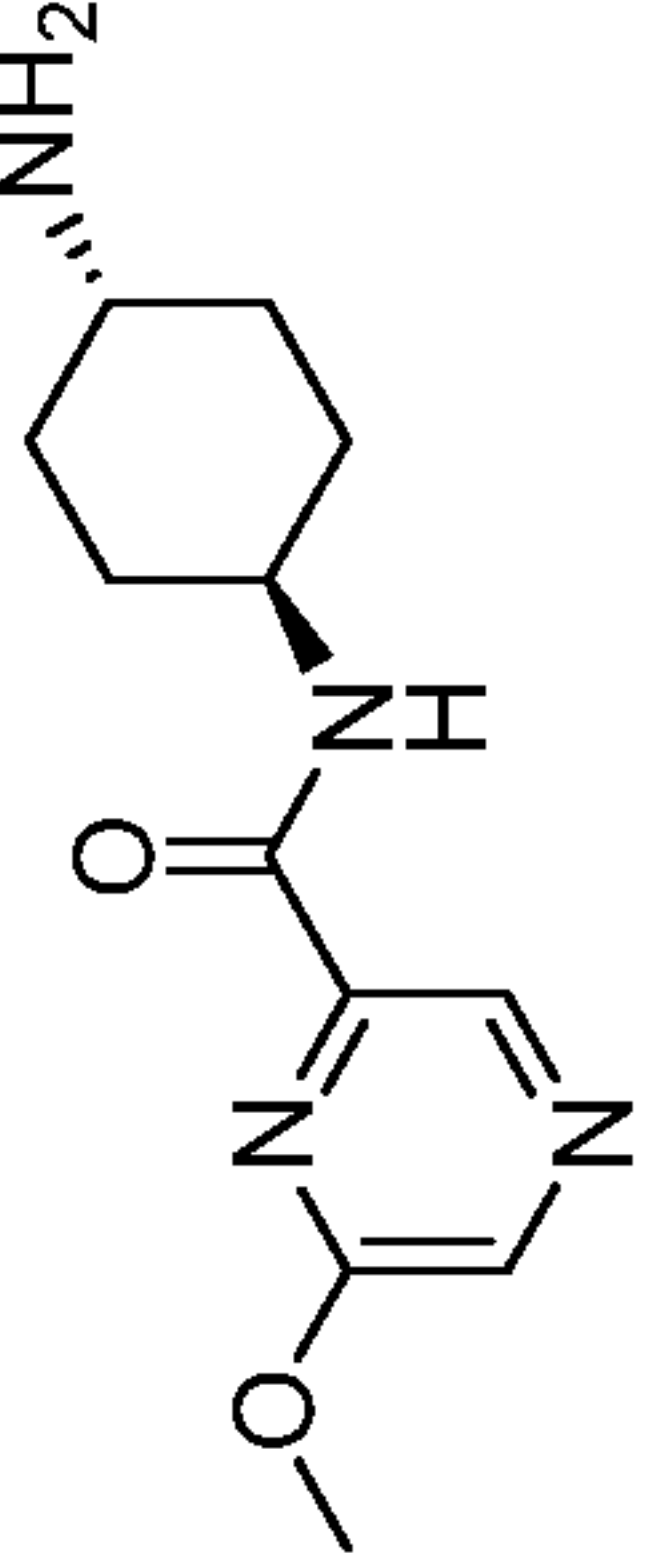
40		HCl	327		HCl
42		HCl	328		None
43		HCl	329		HCl
44		TFA	330		HCl

45		TFA	331		HCl
46		TFA	332		HCl
47		HCl	333		None
48		HCl	334		None
49		HCl	335		None

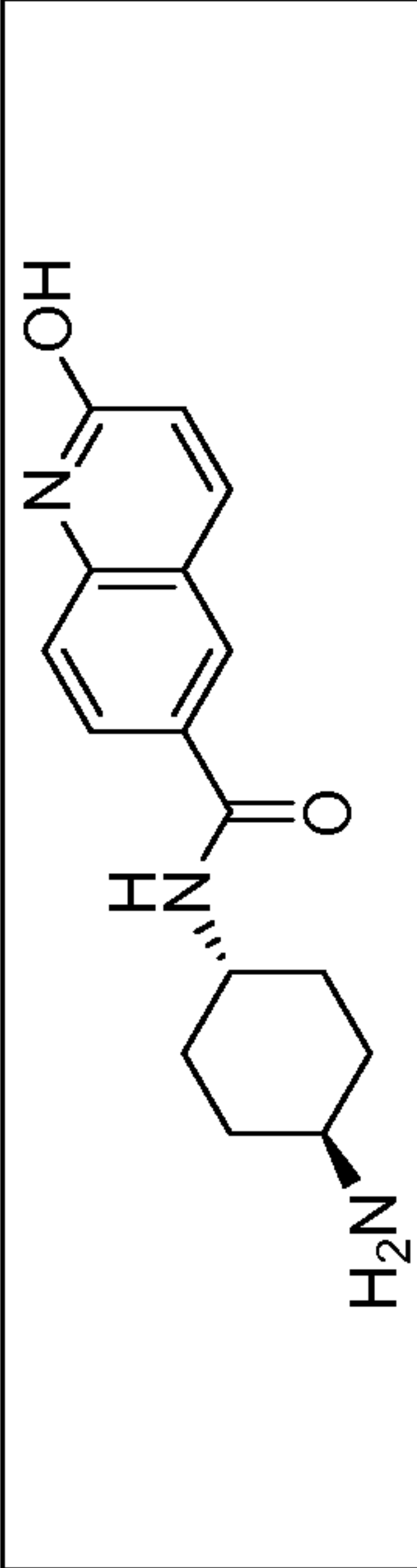
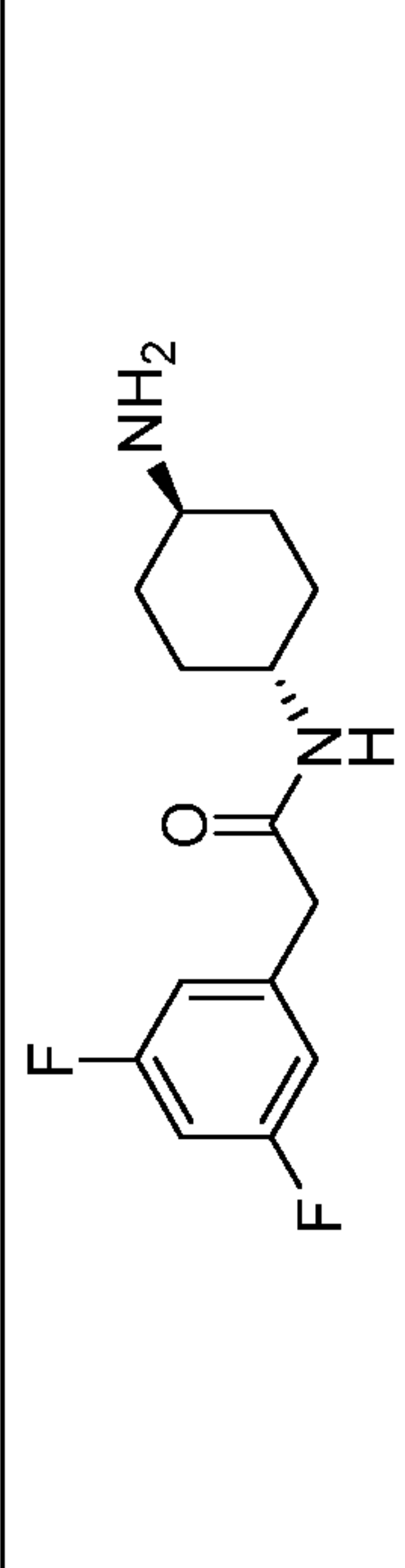
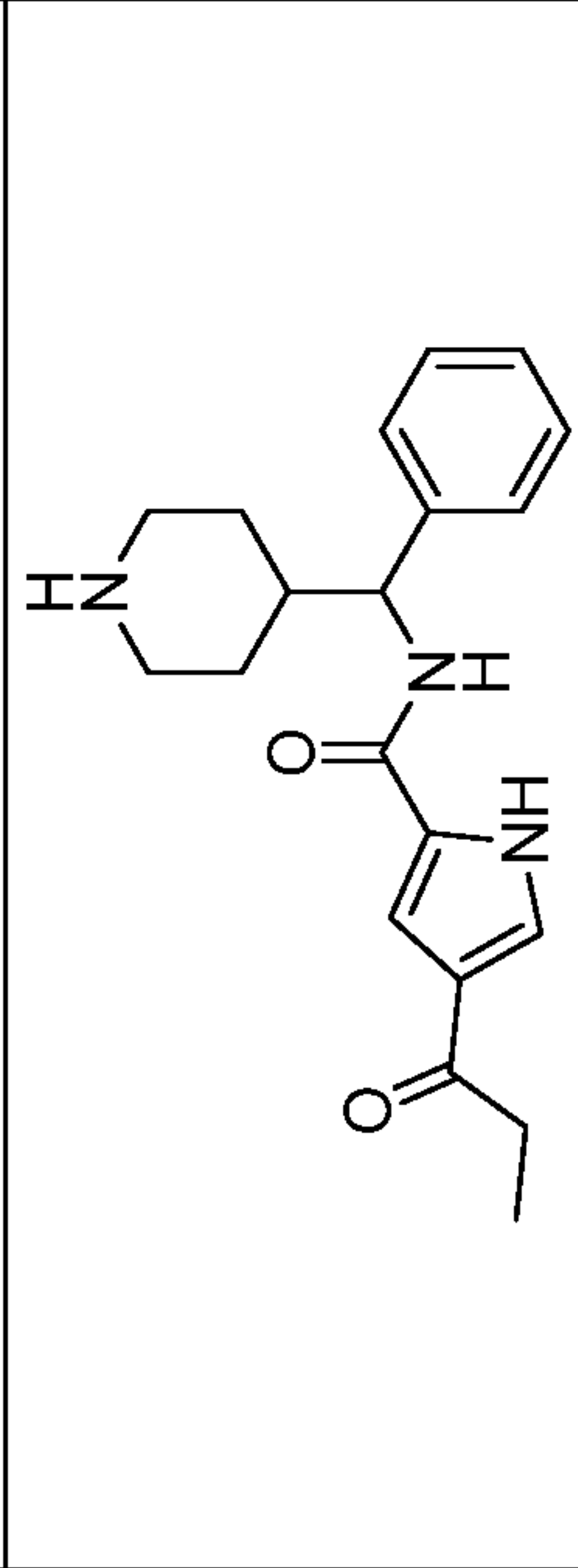
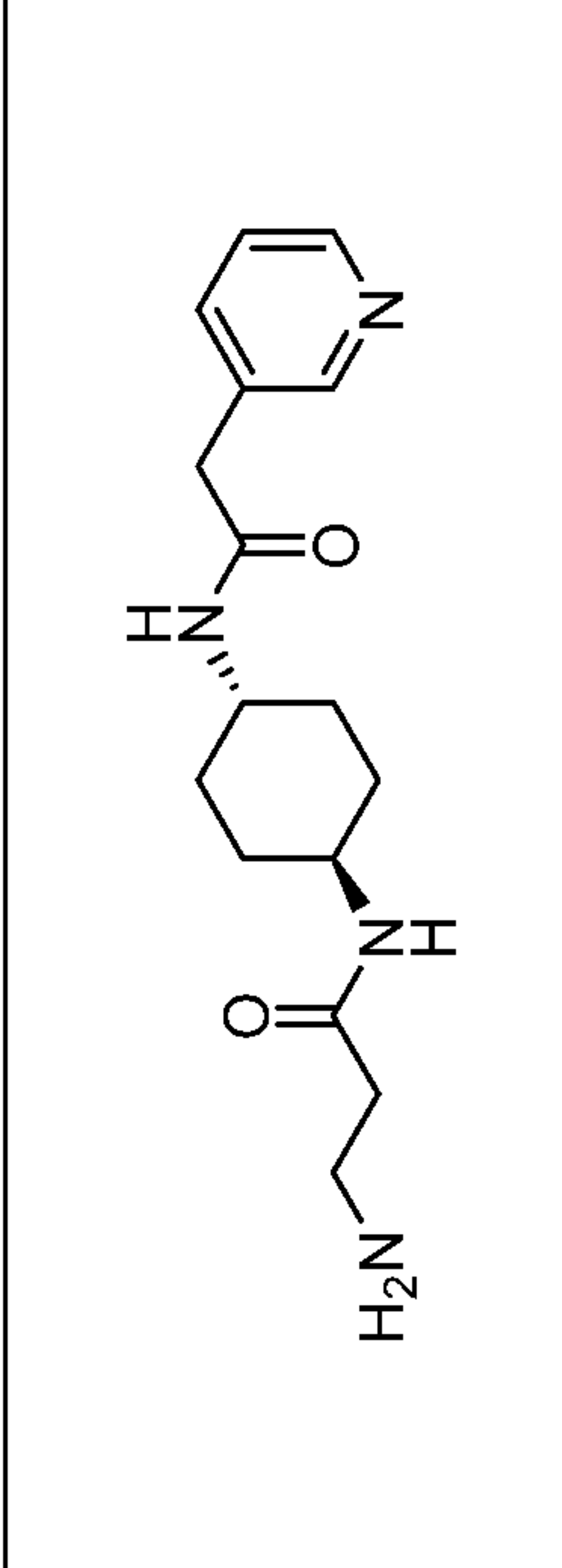
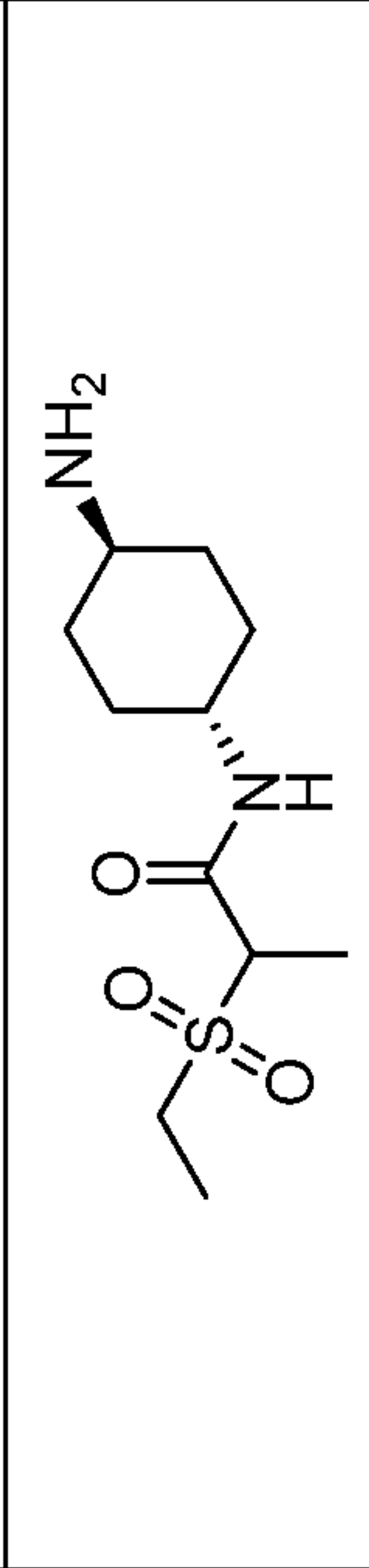
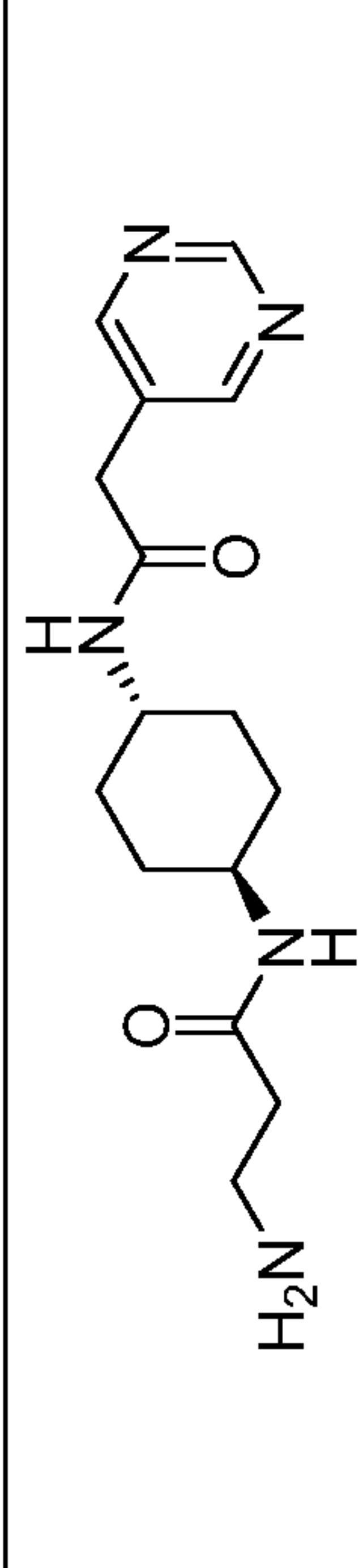
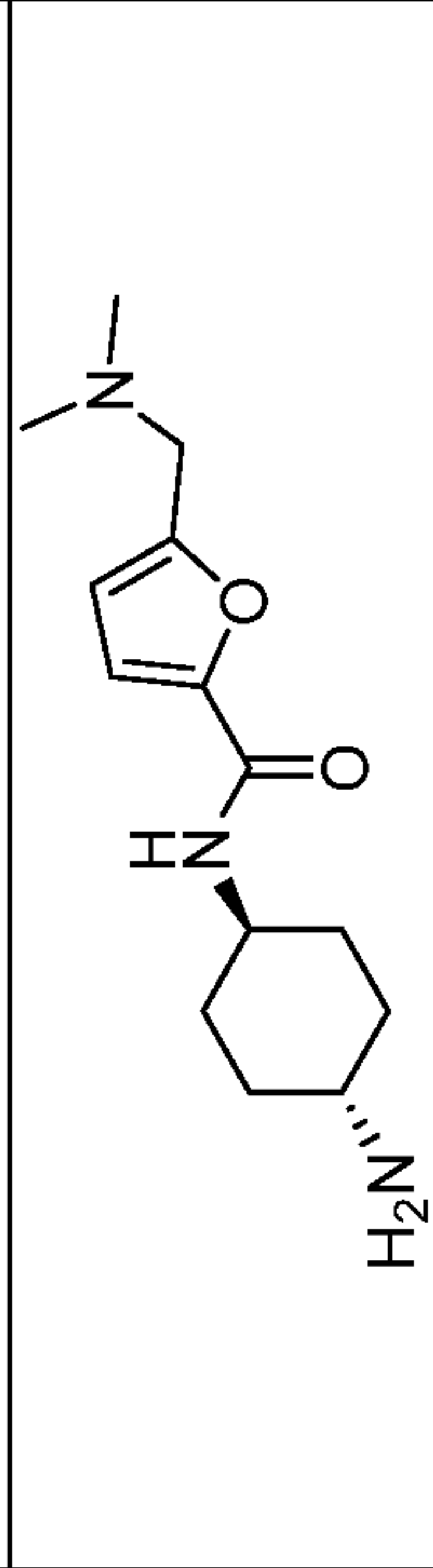
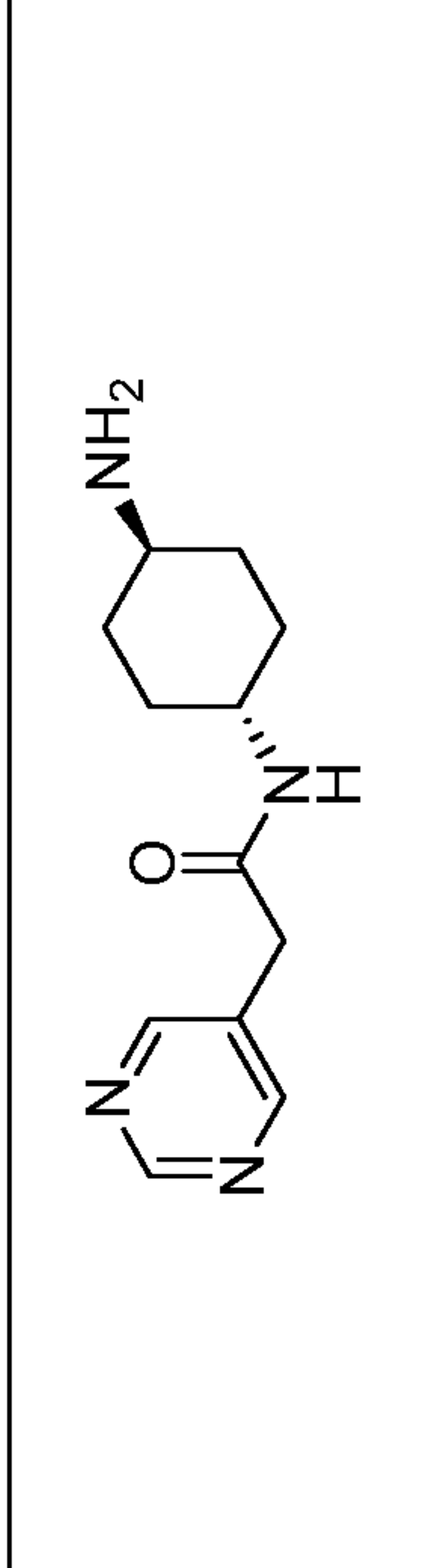
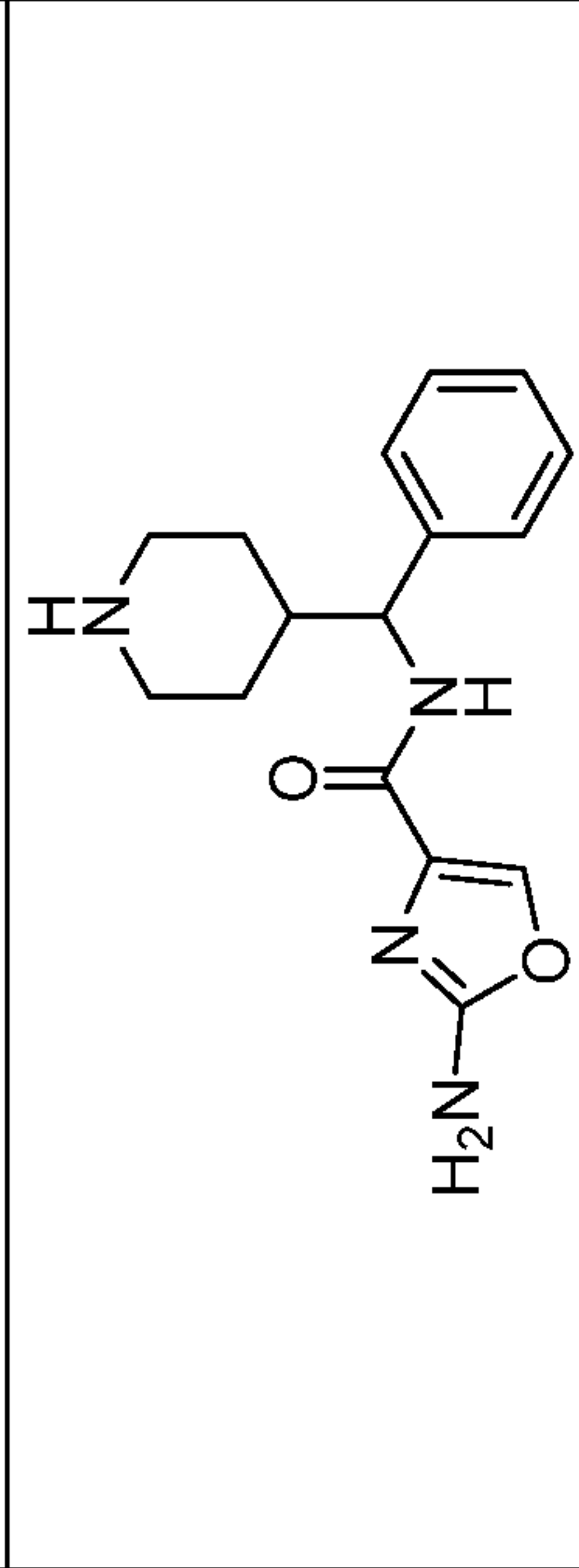
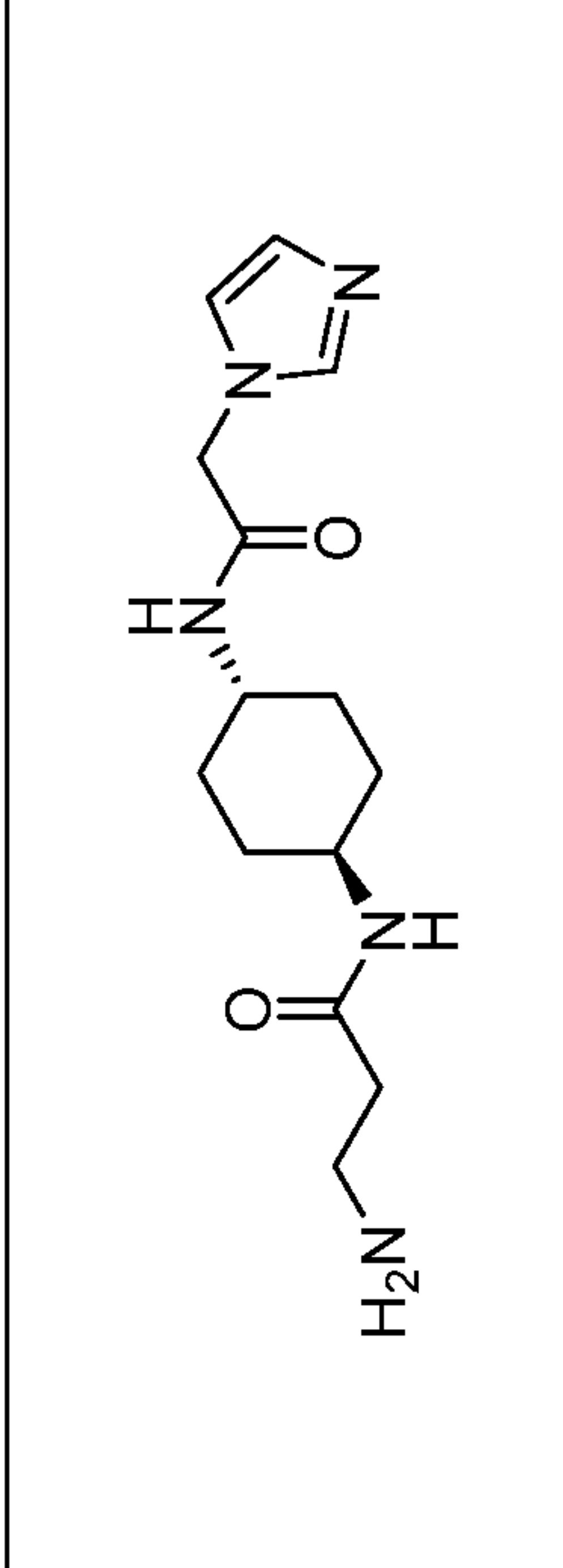
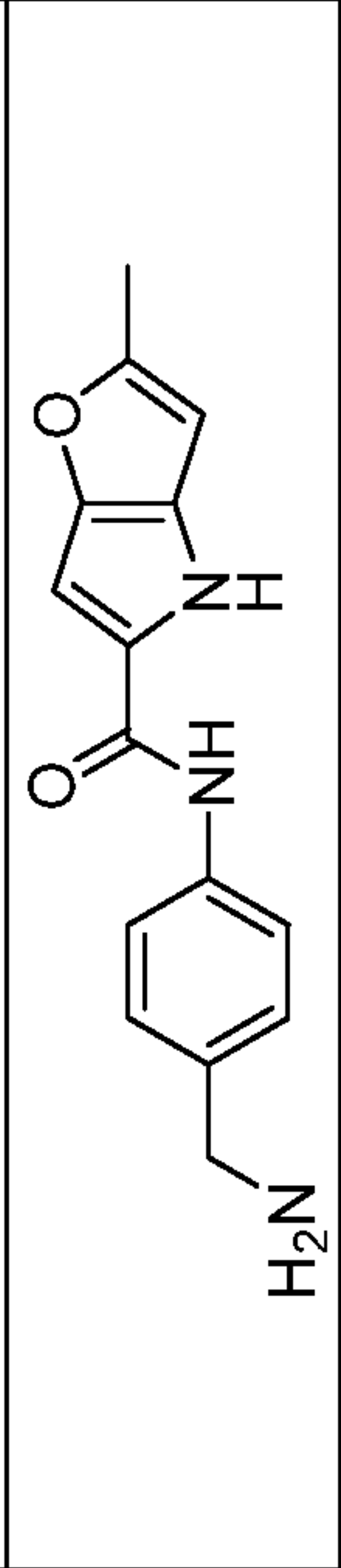
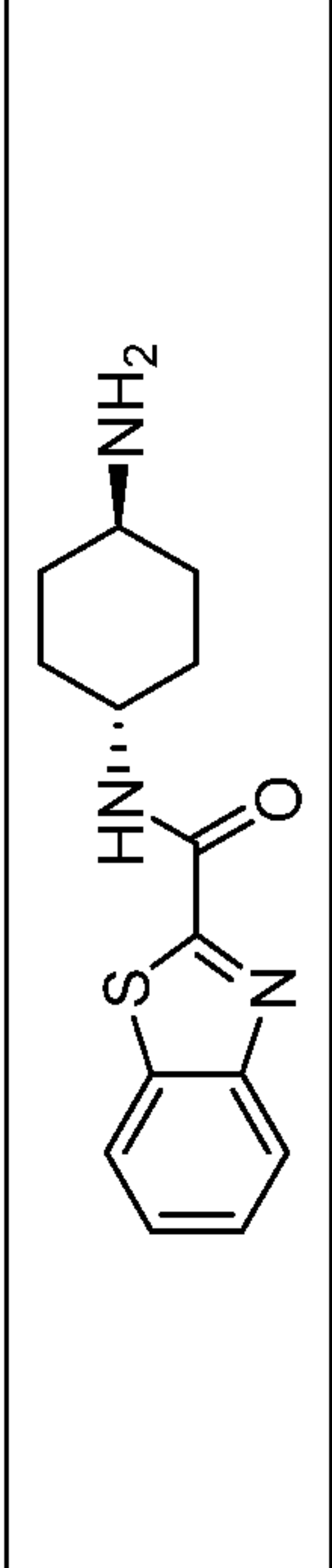
50		HCl	336		None
51		TFA	337		None
52		HCl	338		TFA
53		HCl	339		None
54		HCl	340		HCl

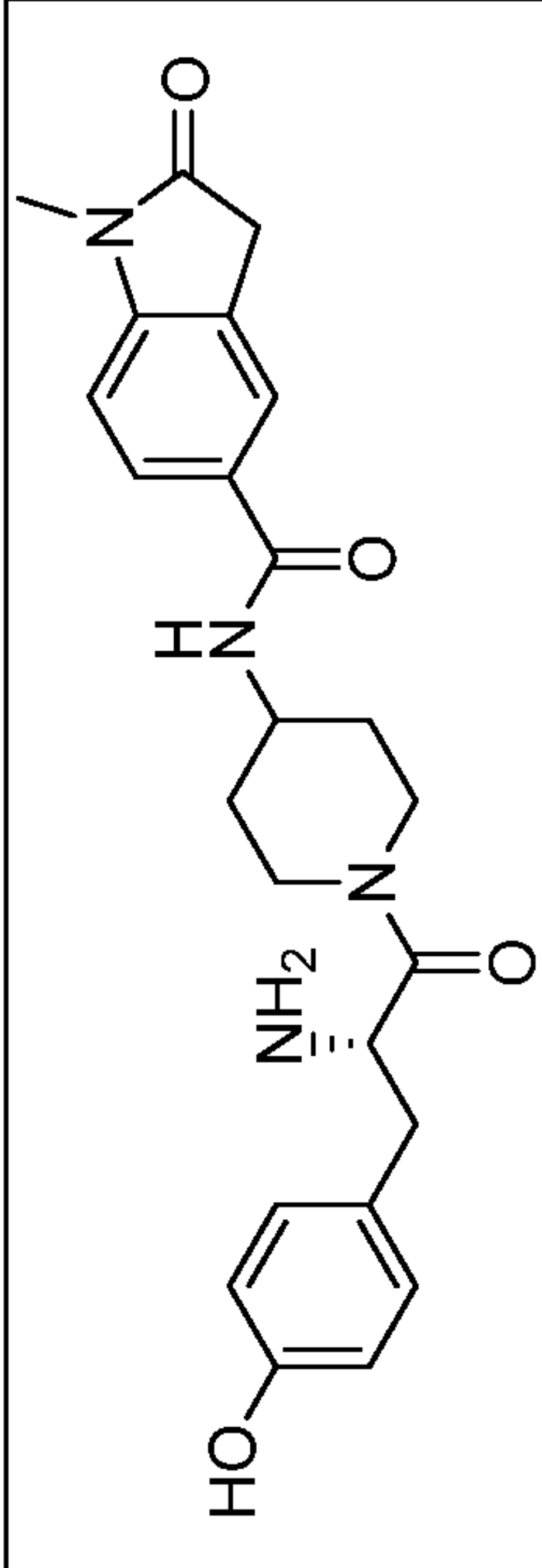
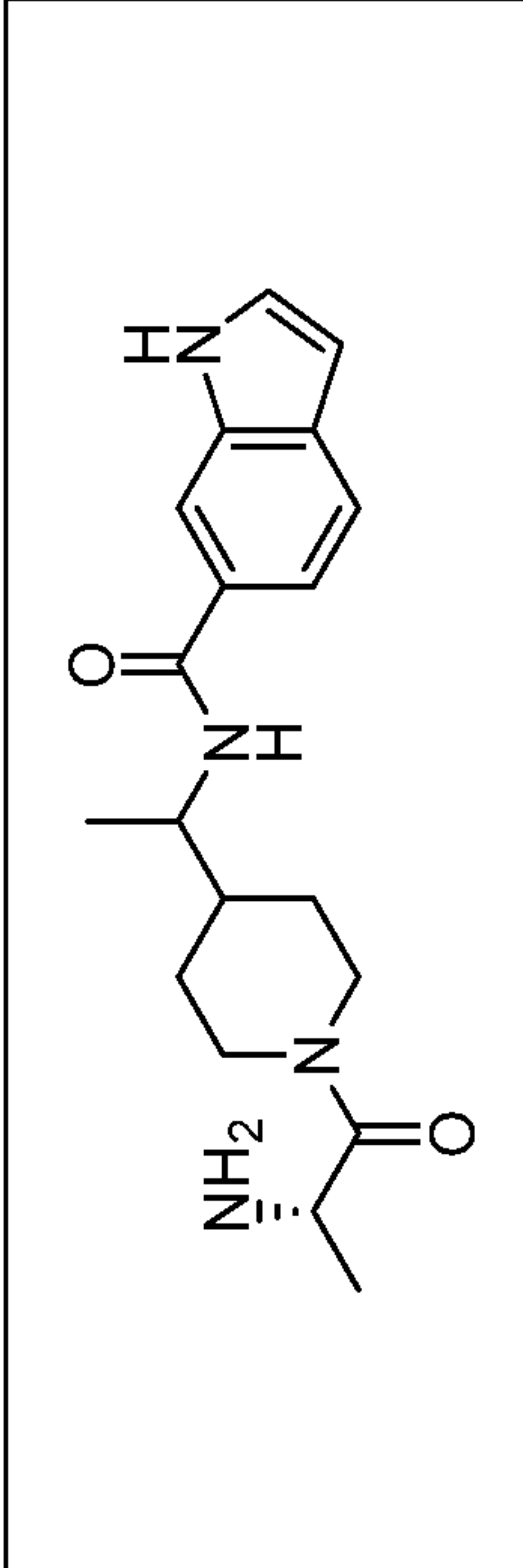
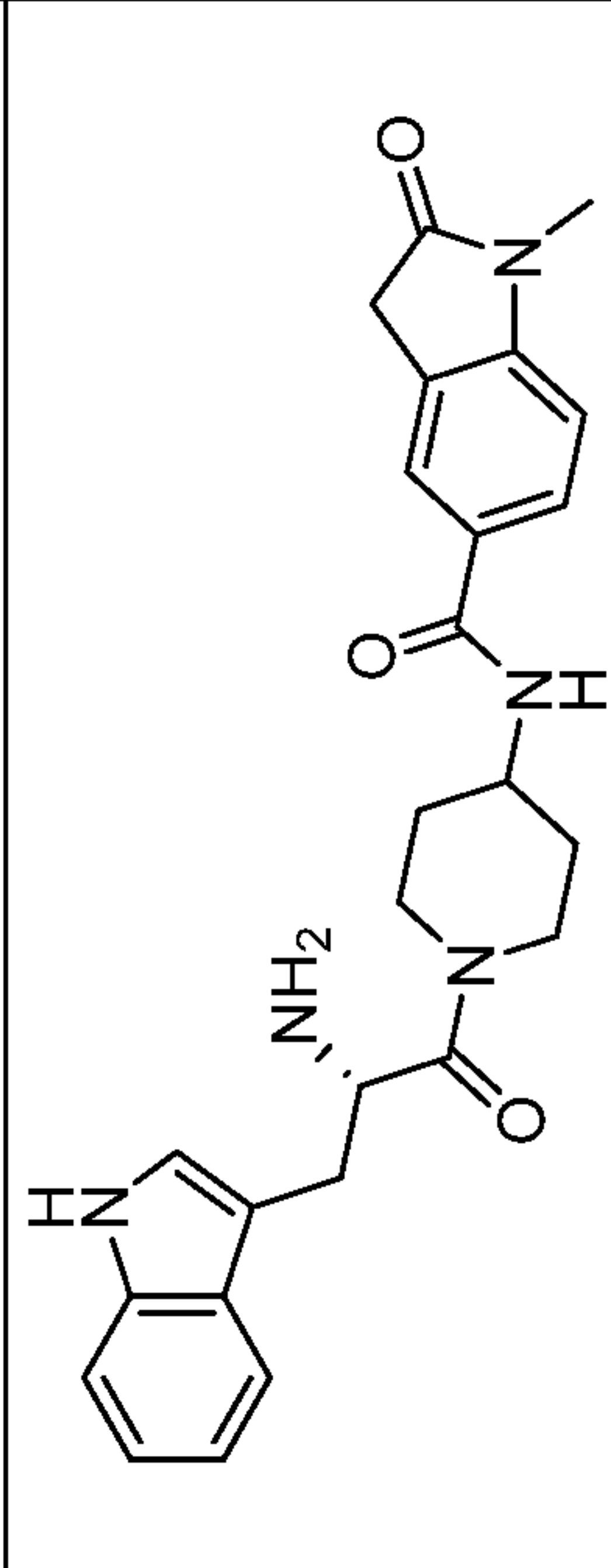
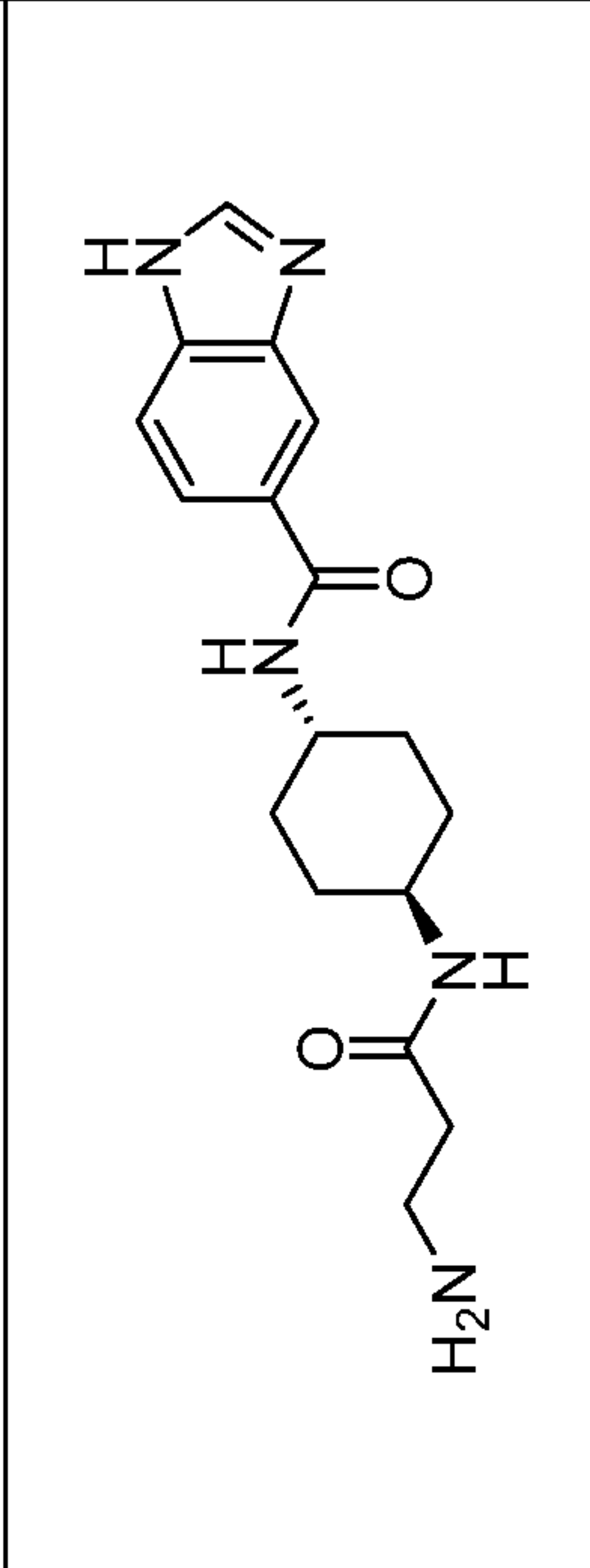
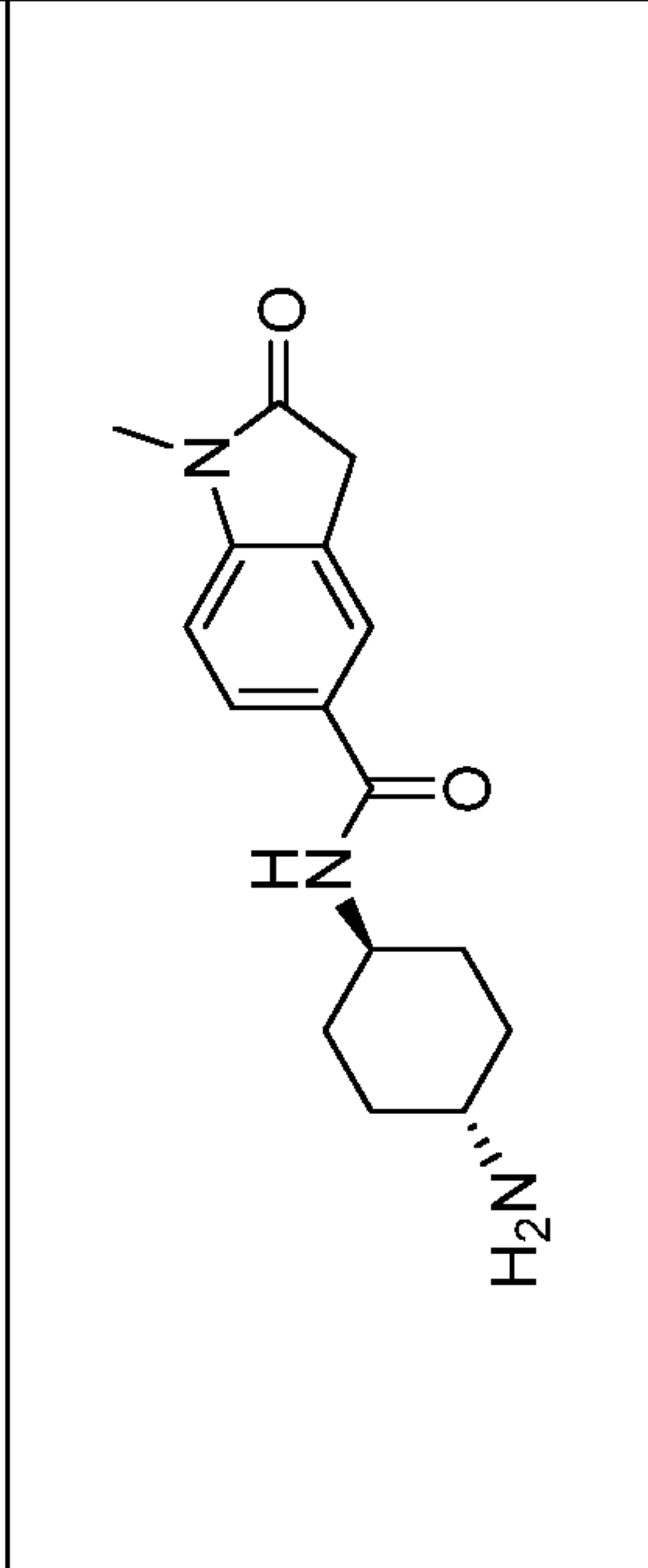
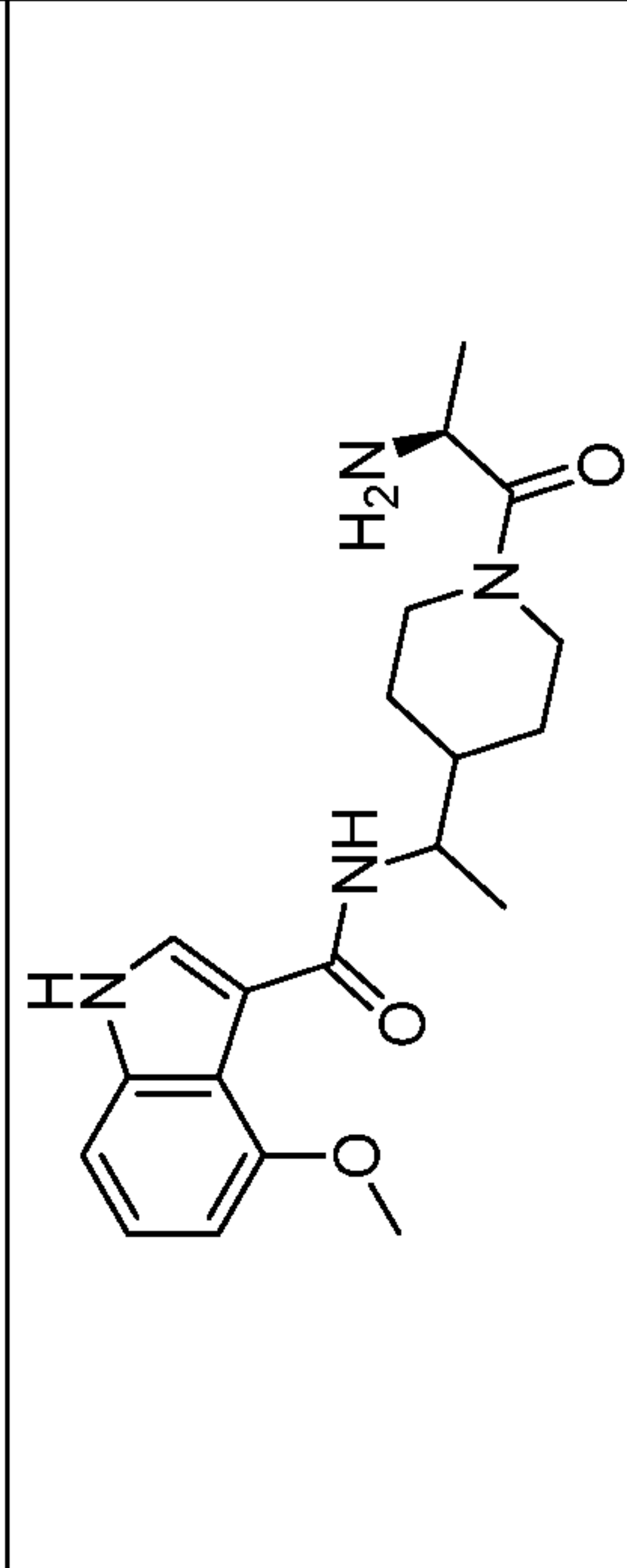
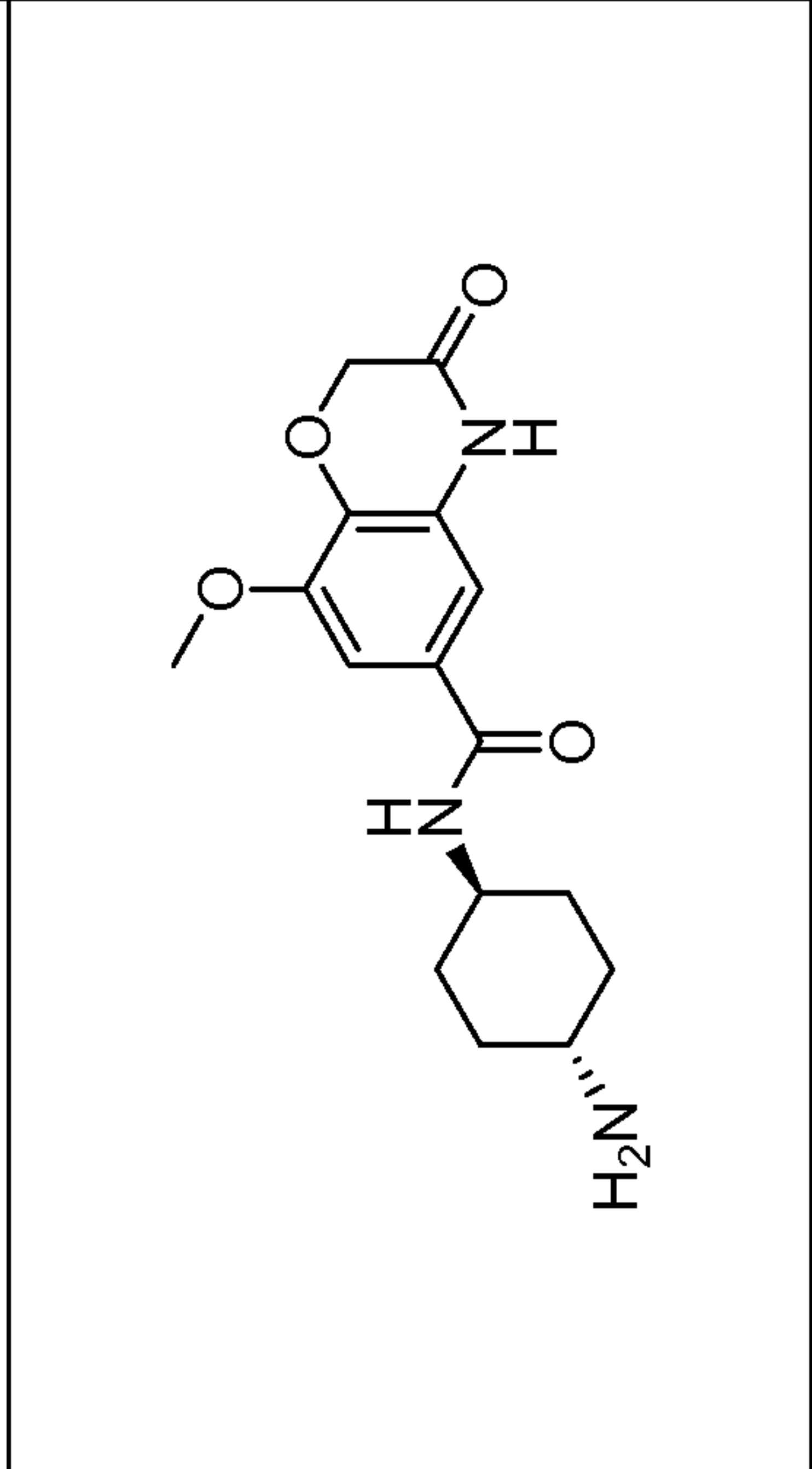
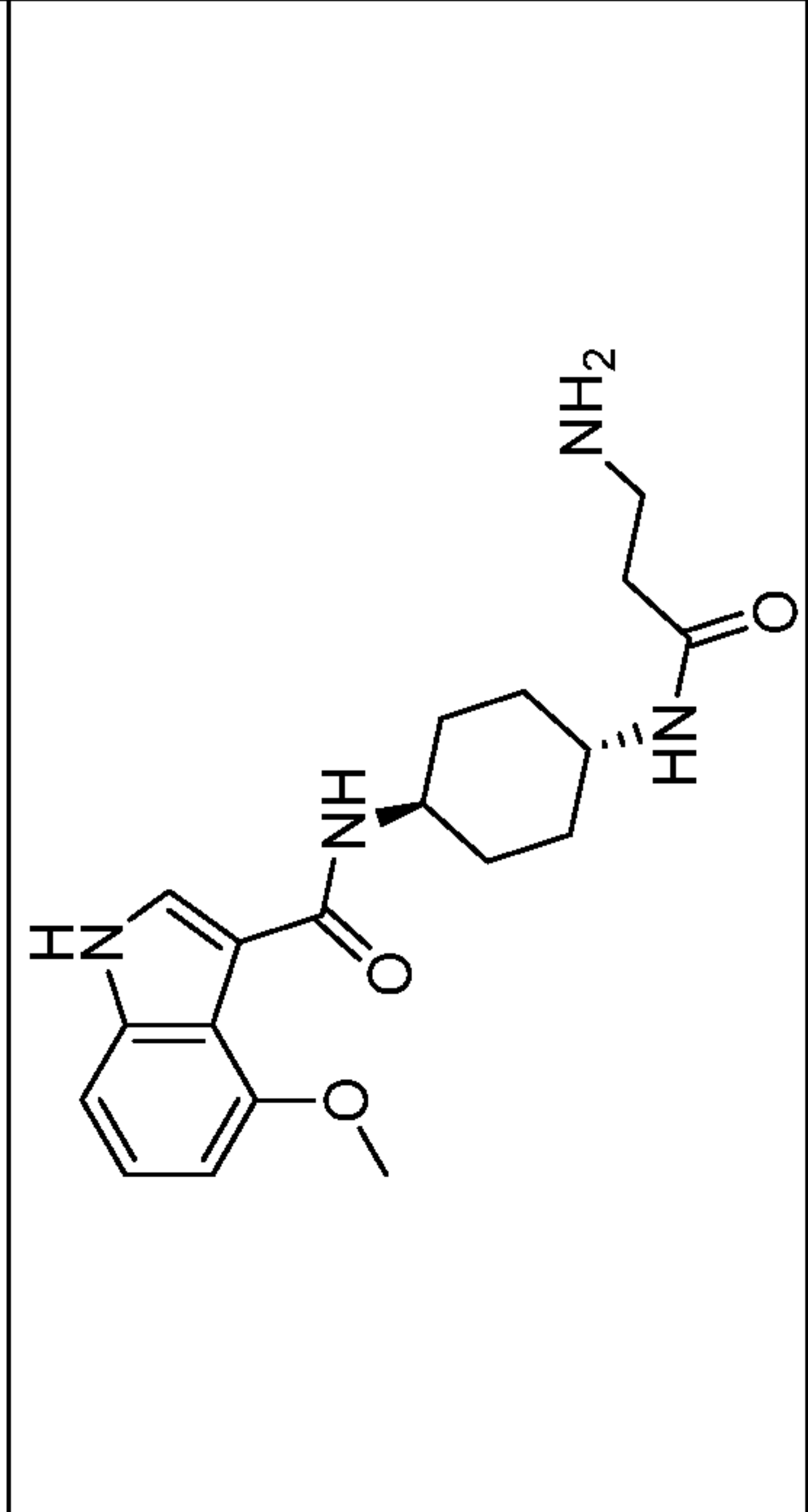
55		HCl	341		TFA
56		HCl	342		TFA
57		HCl	343		TFA
58		HCl	344		HCl
59		HCl	345		HCl

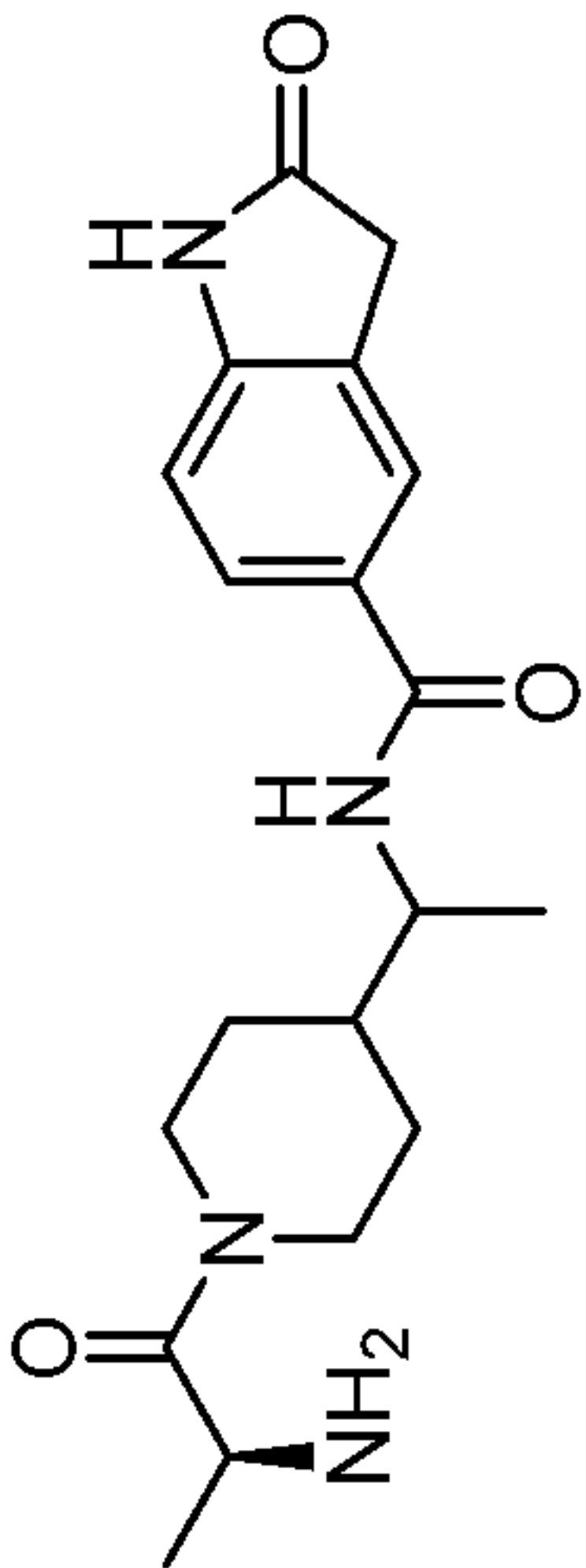
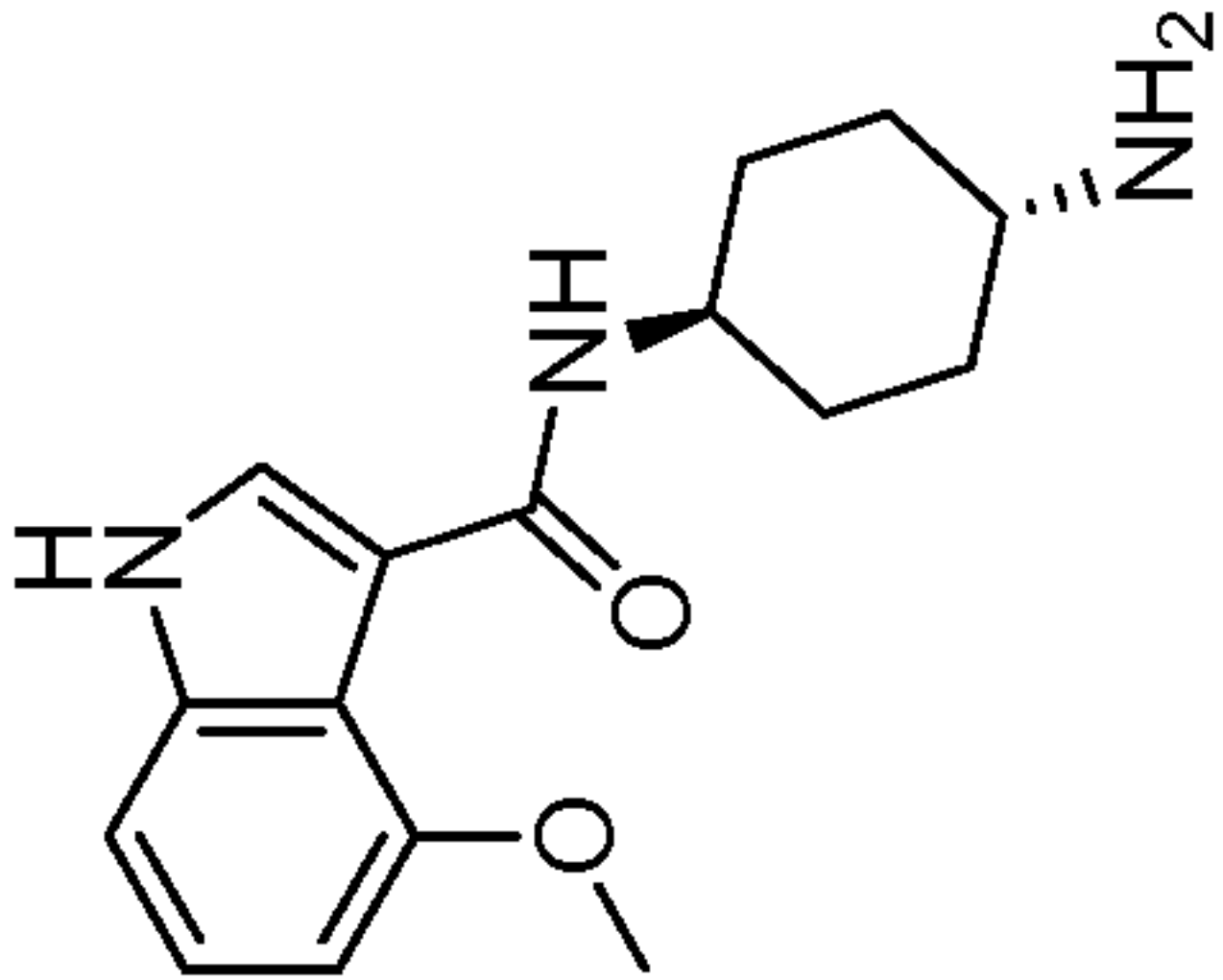
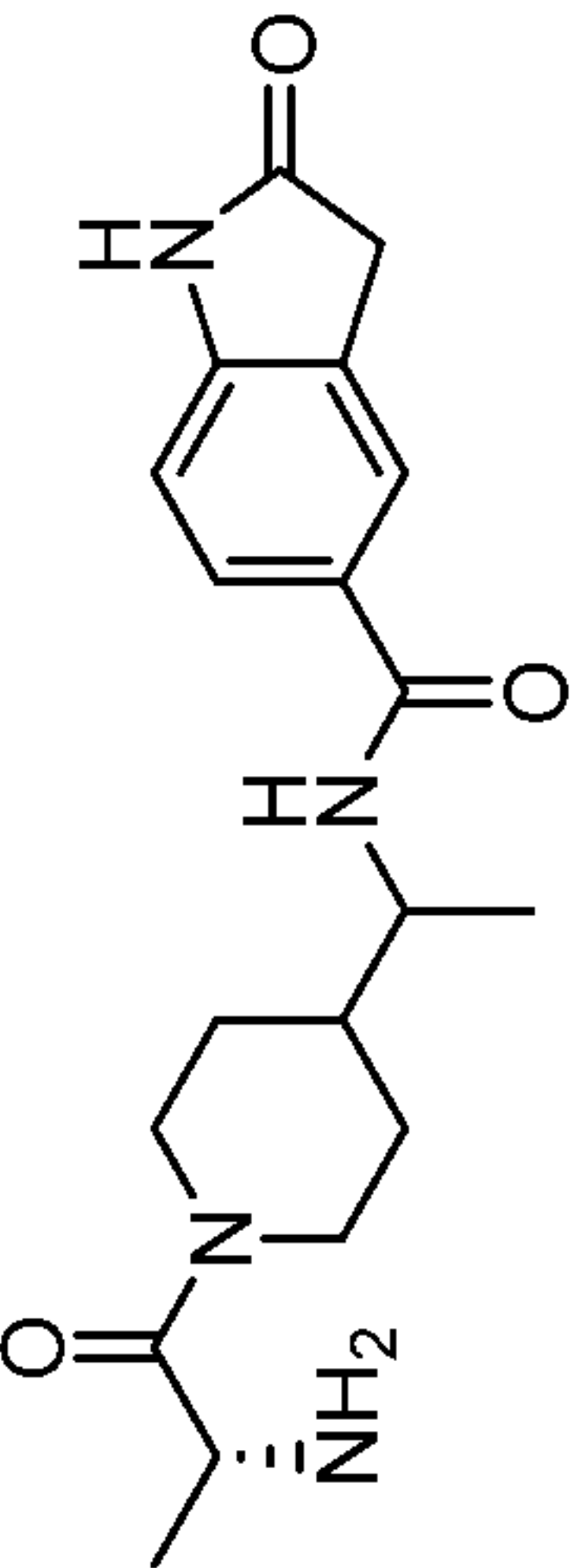
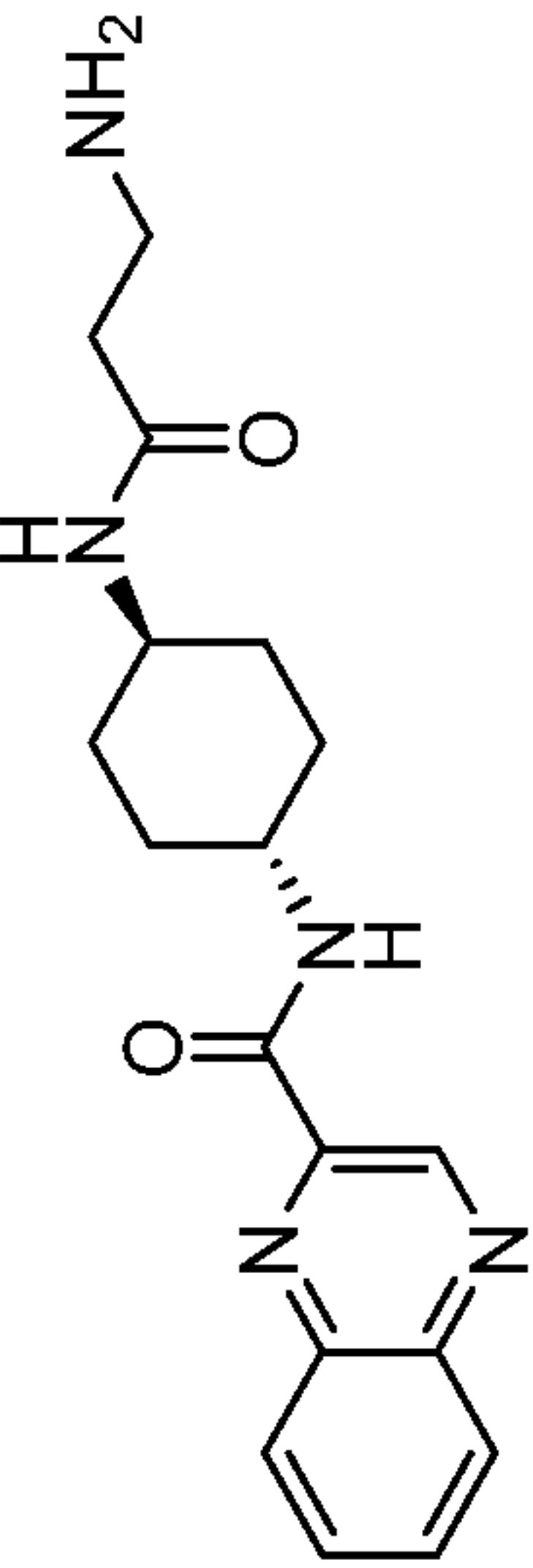
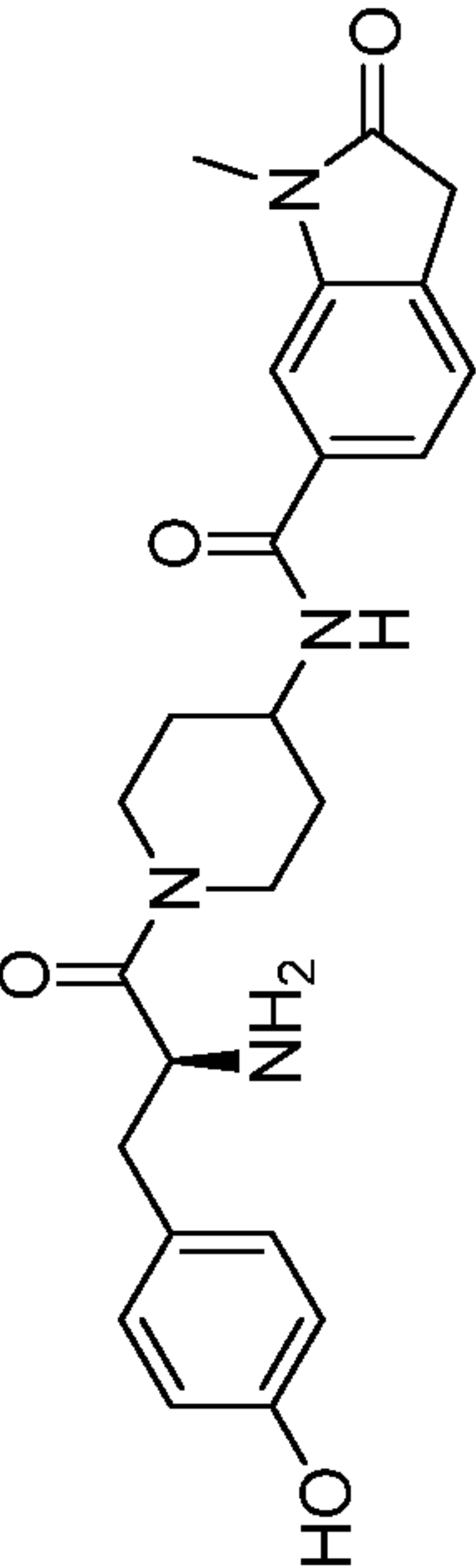
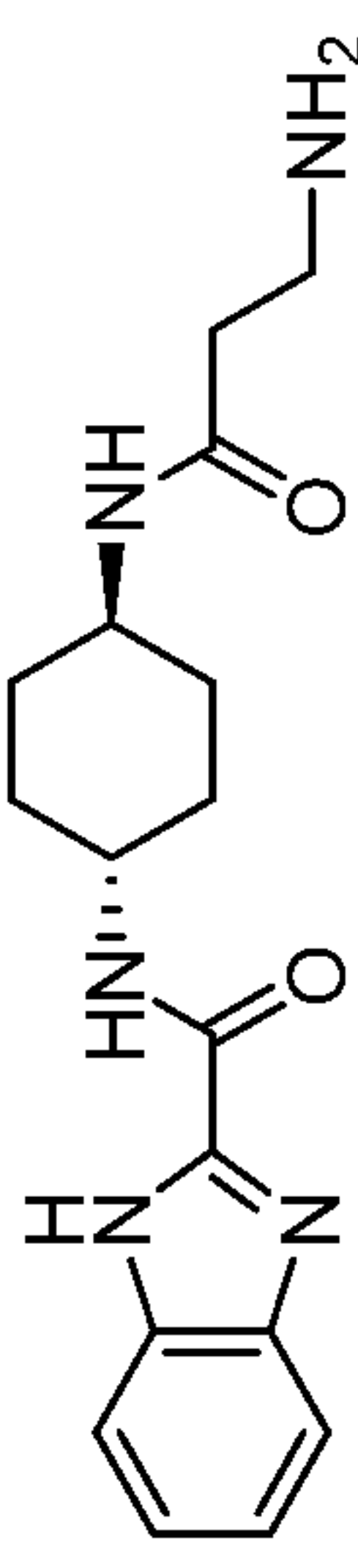
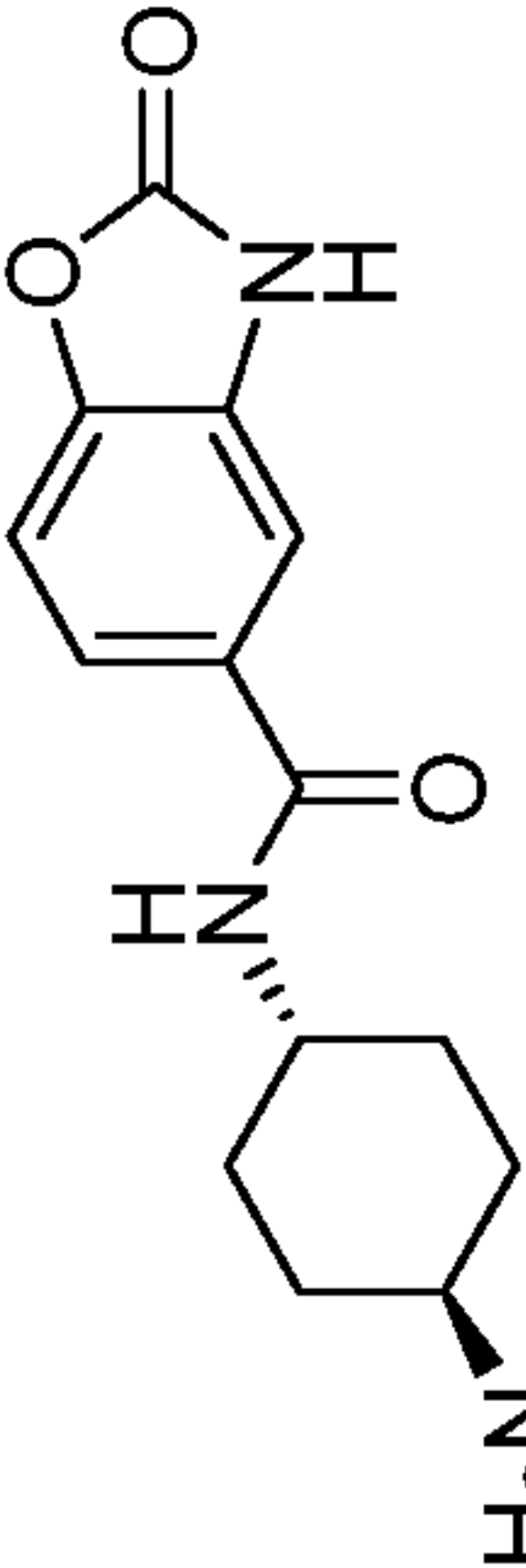
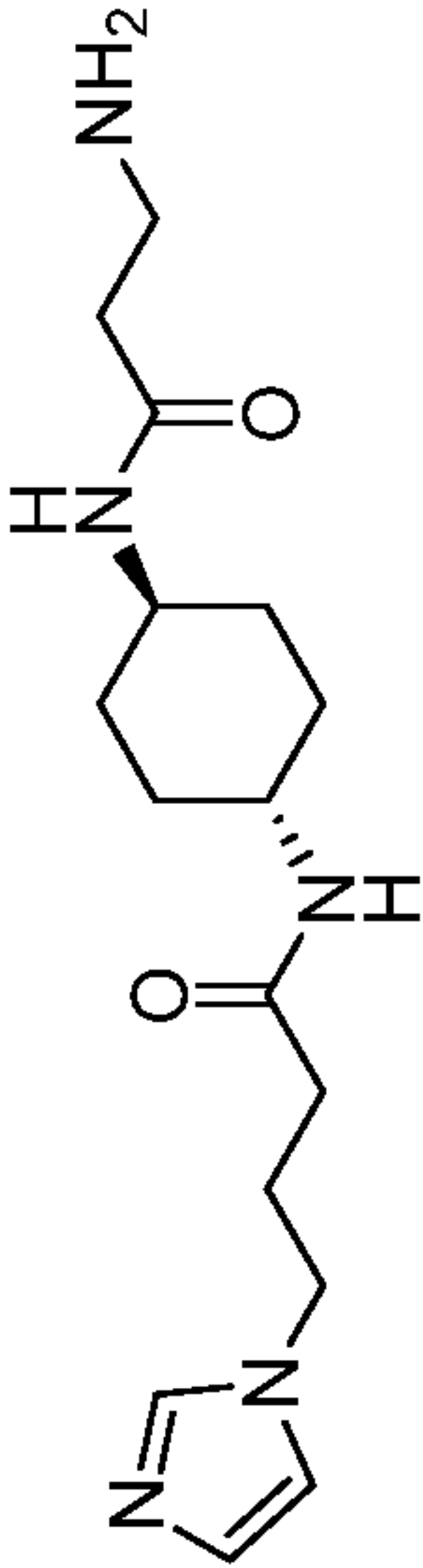
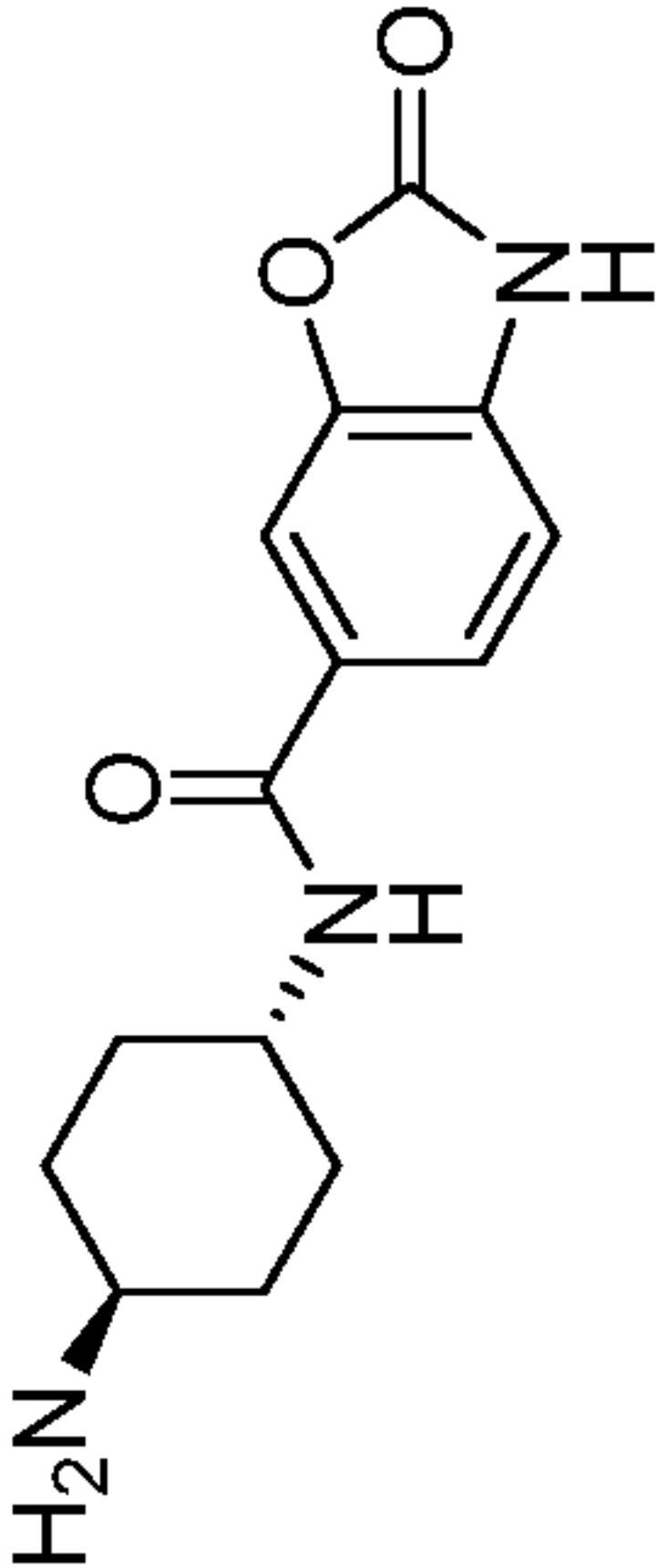
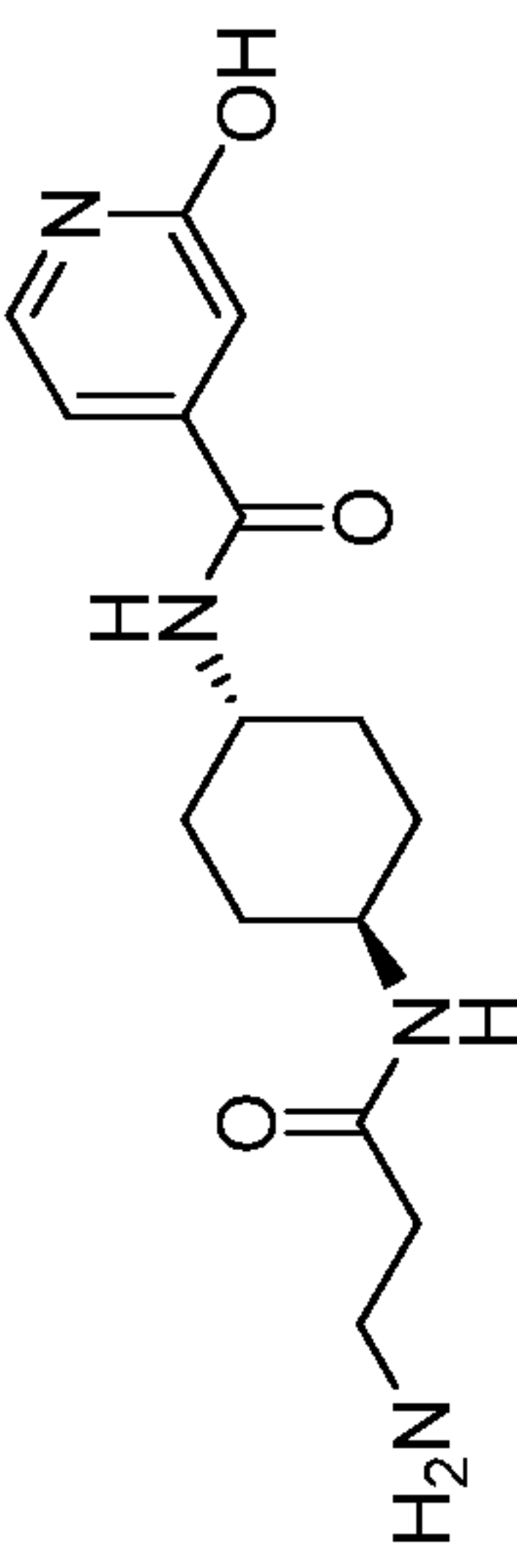
60		HCl	346		HCl
61		HCl	347		HCl
62		HCl	348		TFA
63		HCl	349		TFA
64		HCl	350		TFA

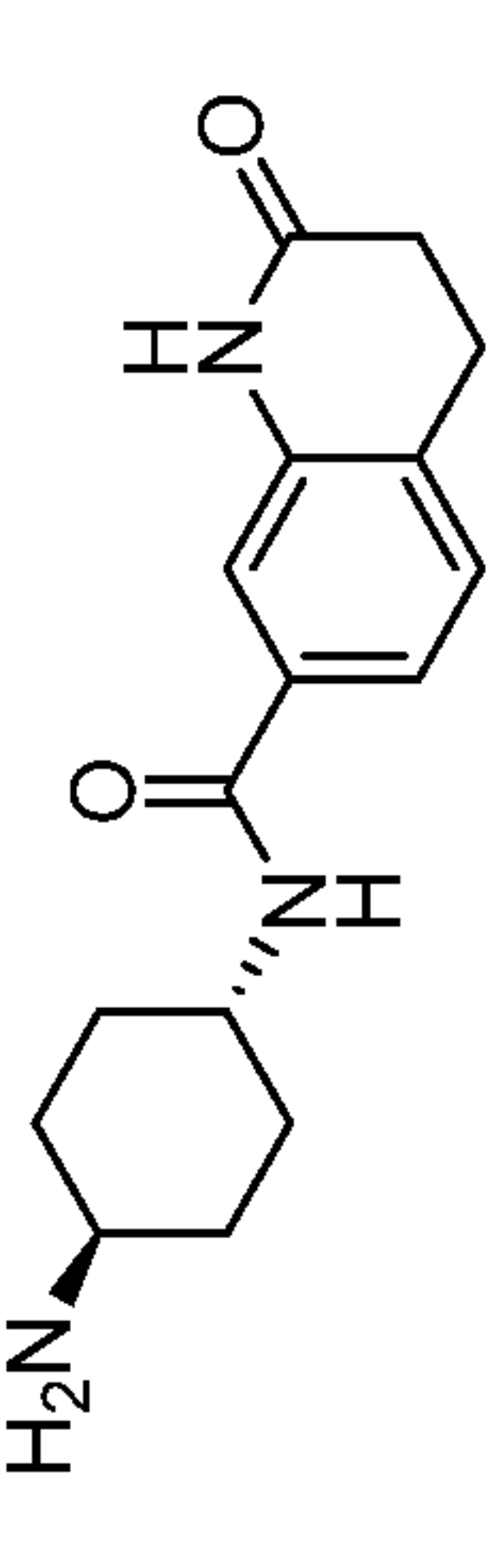
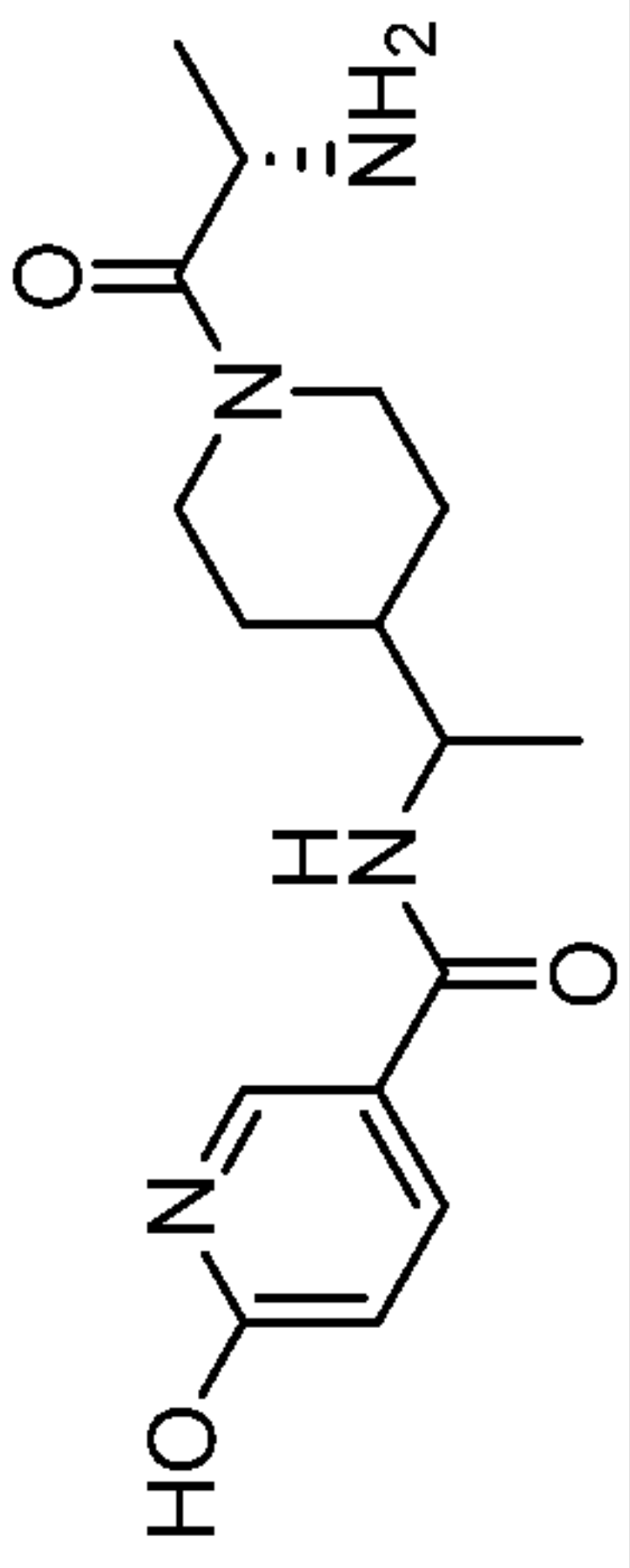
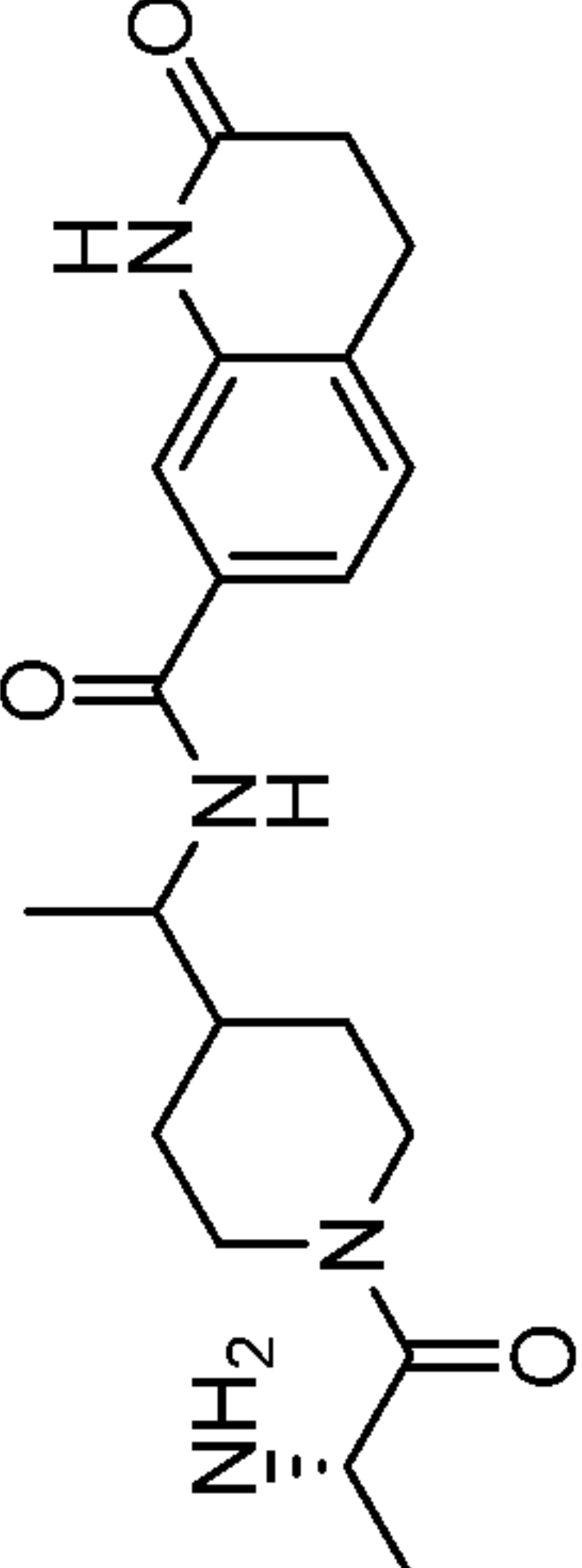
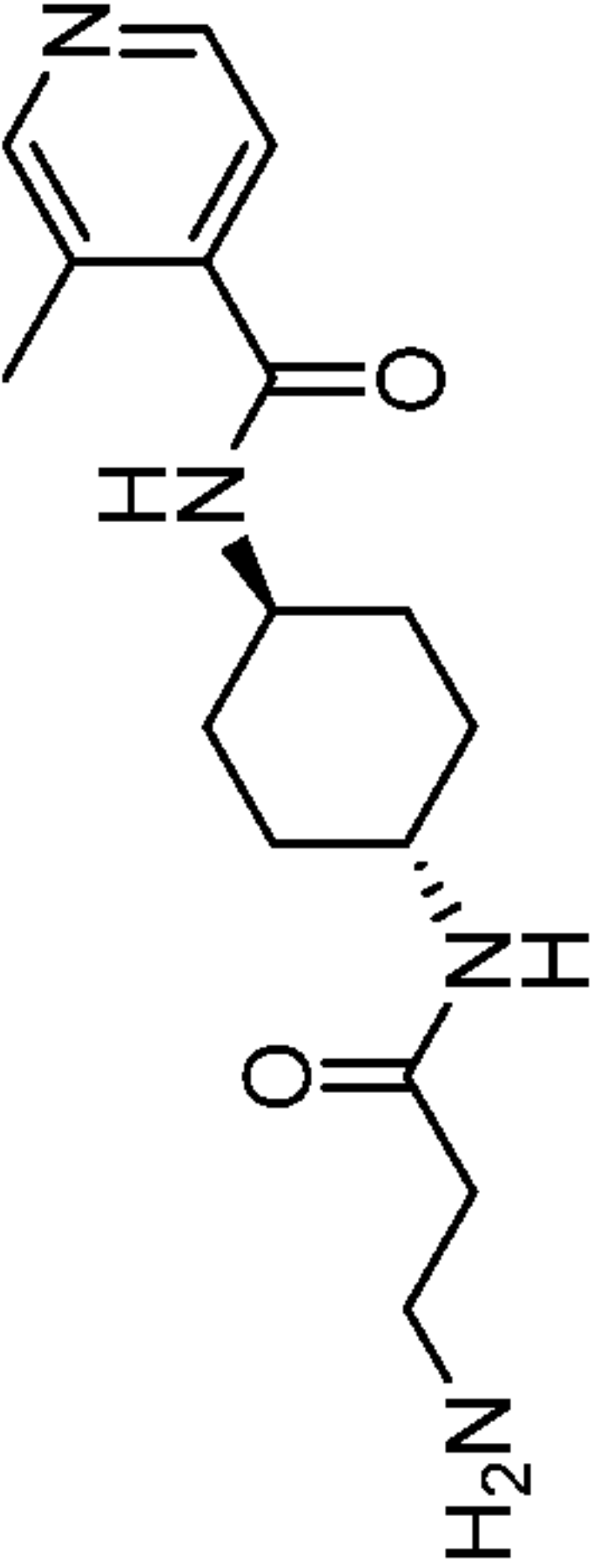
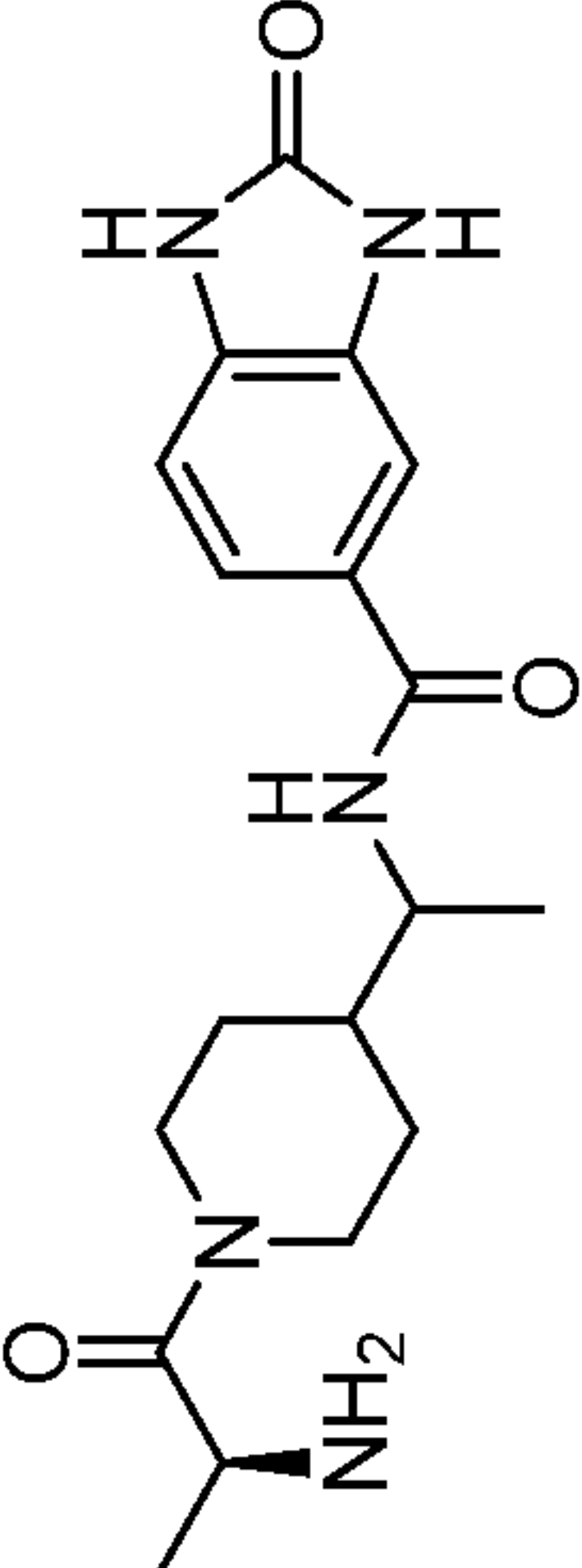
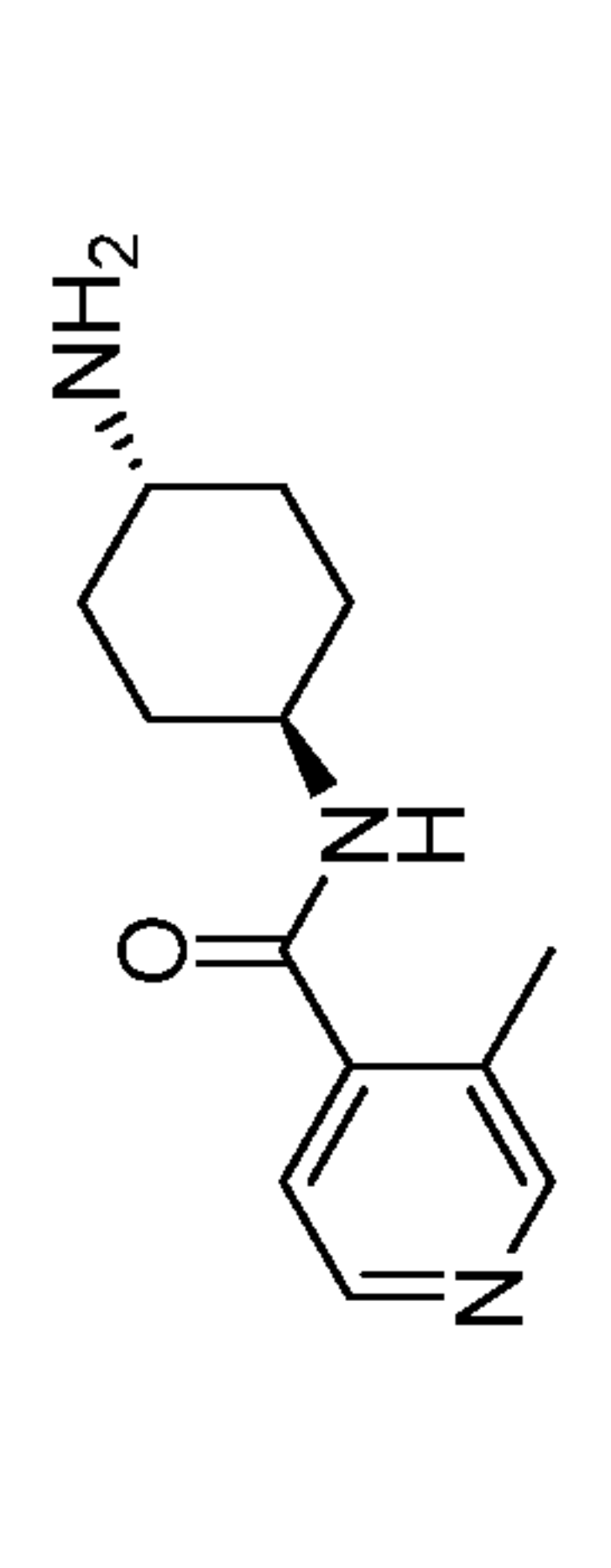
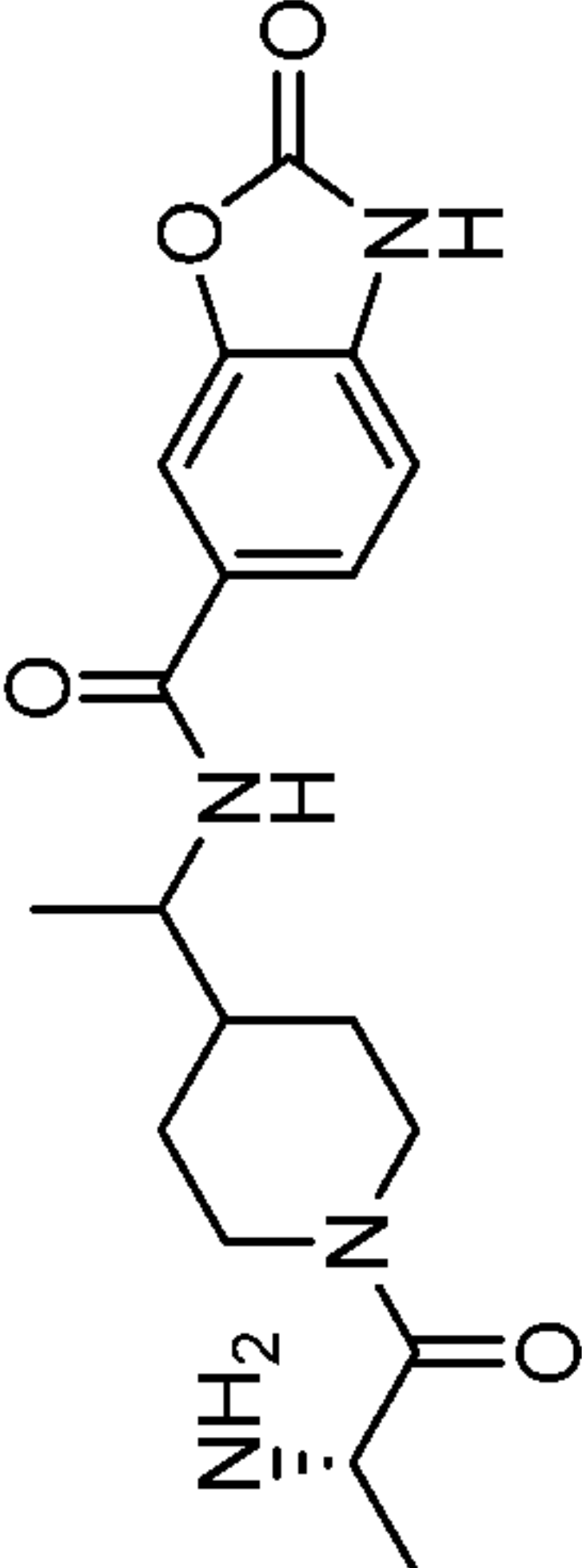
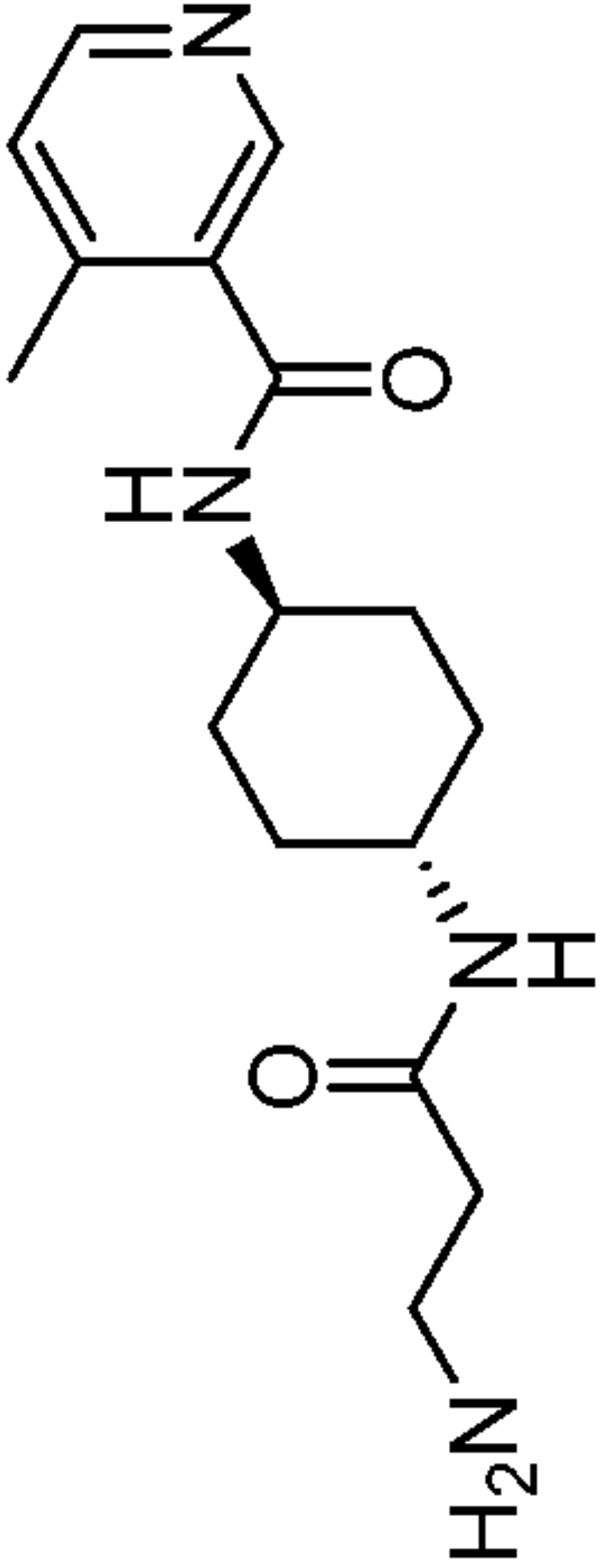
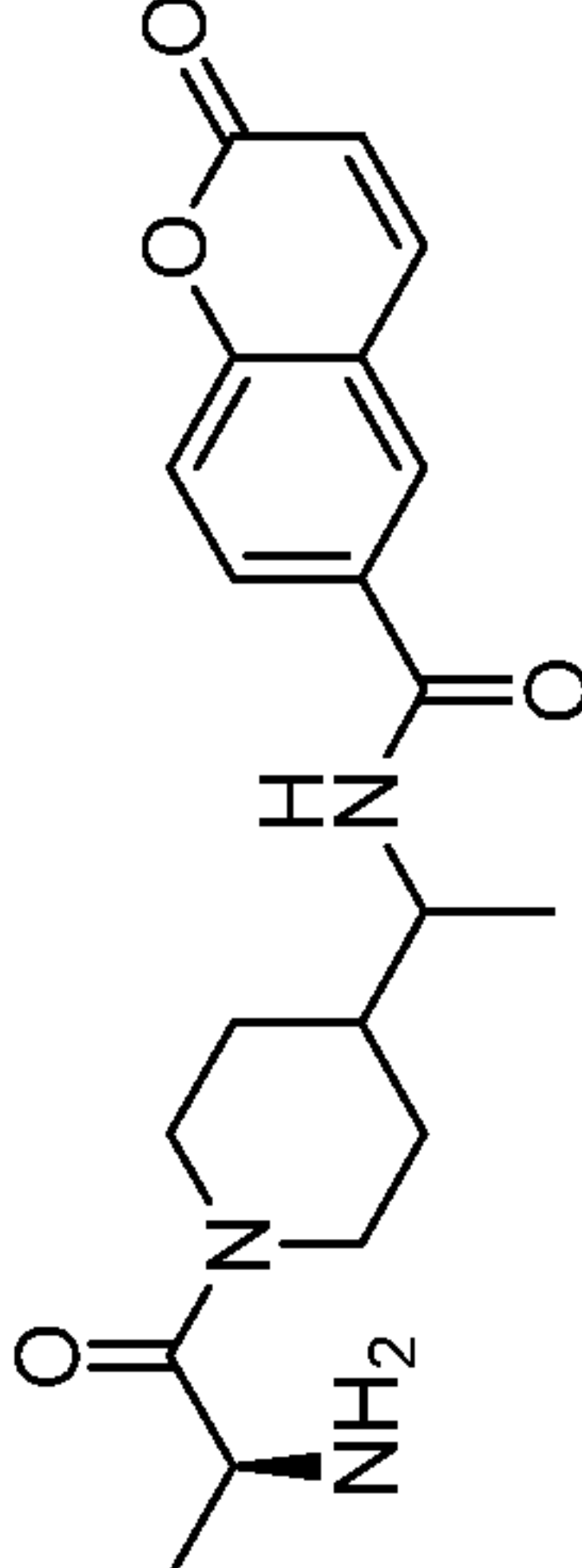
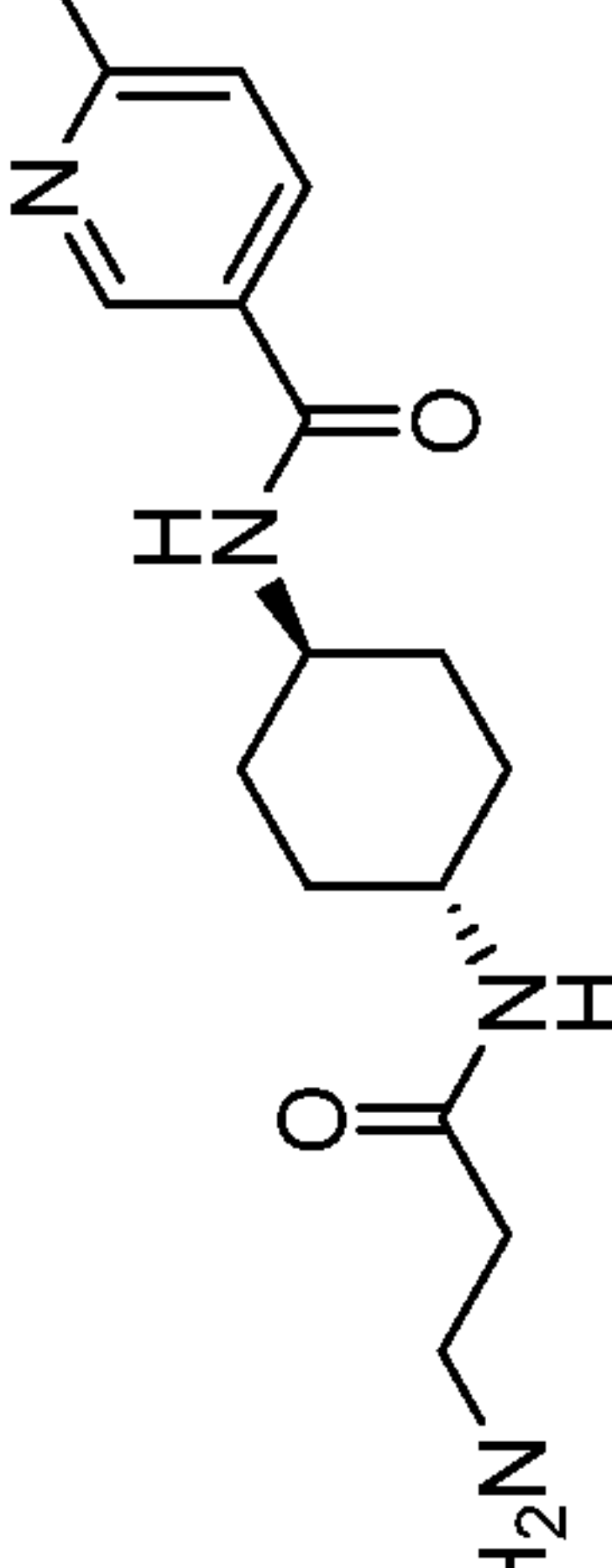
65		HCl	351		HCl
66		HCl	352		HCl
67		HCl	353		HCl
68		HCl	354		HCl
69		TFA	355		HCl
70		TFA	356		HCl

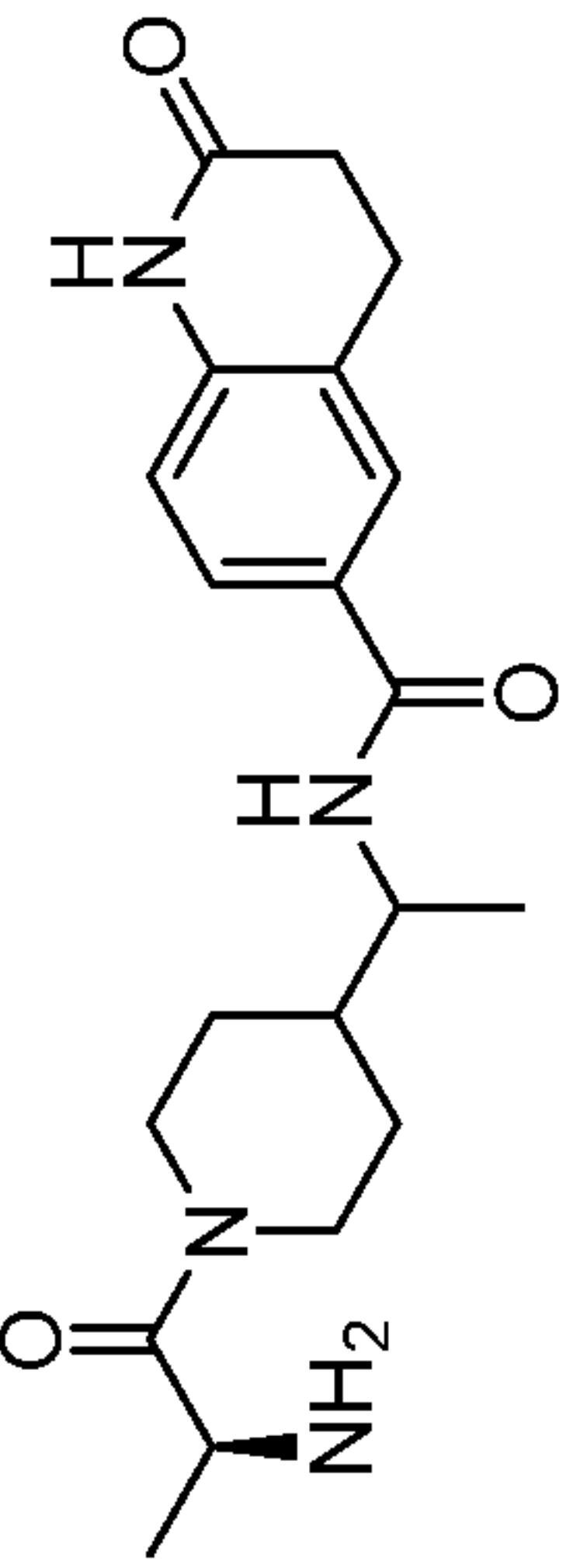
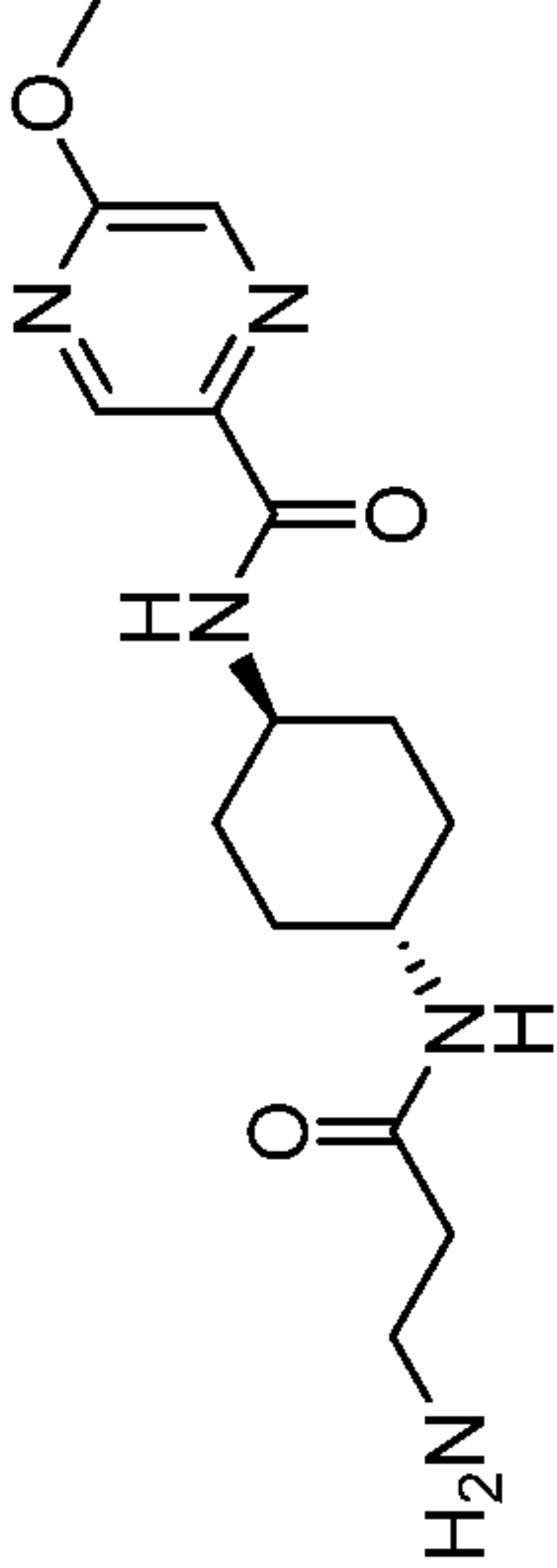
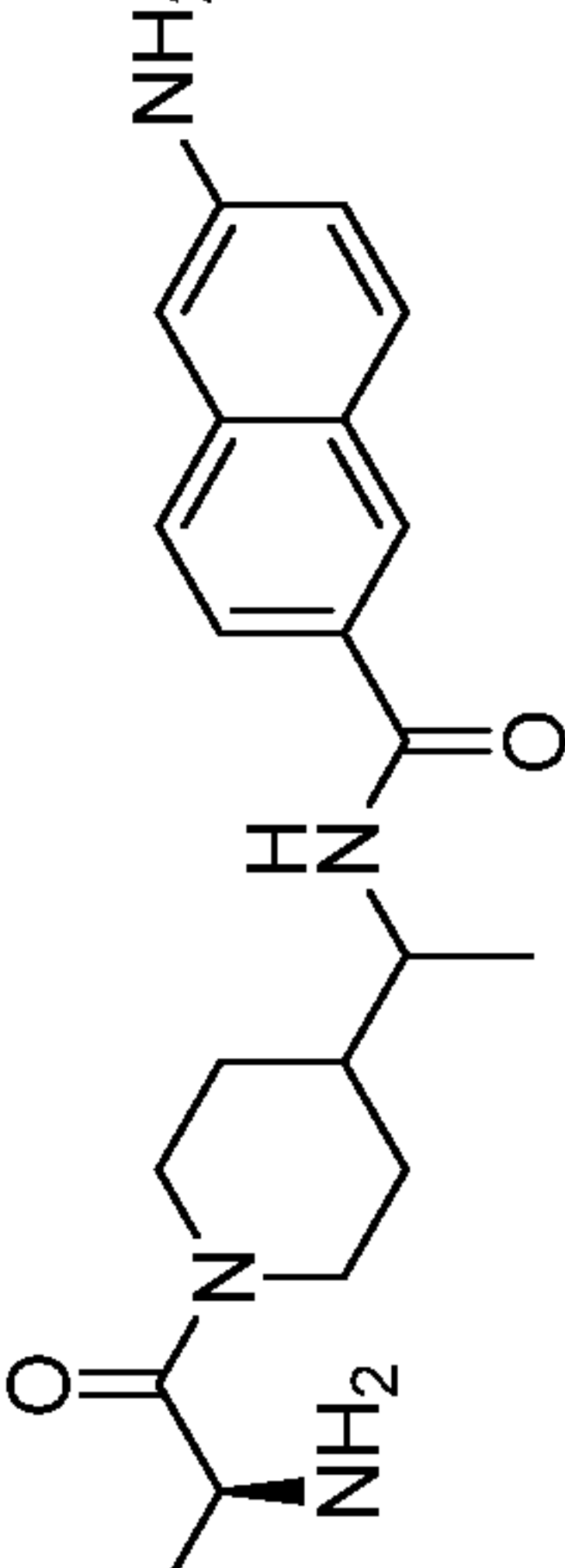
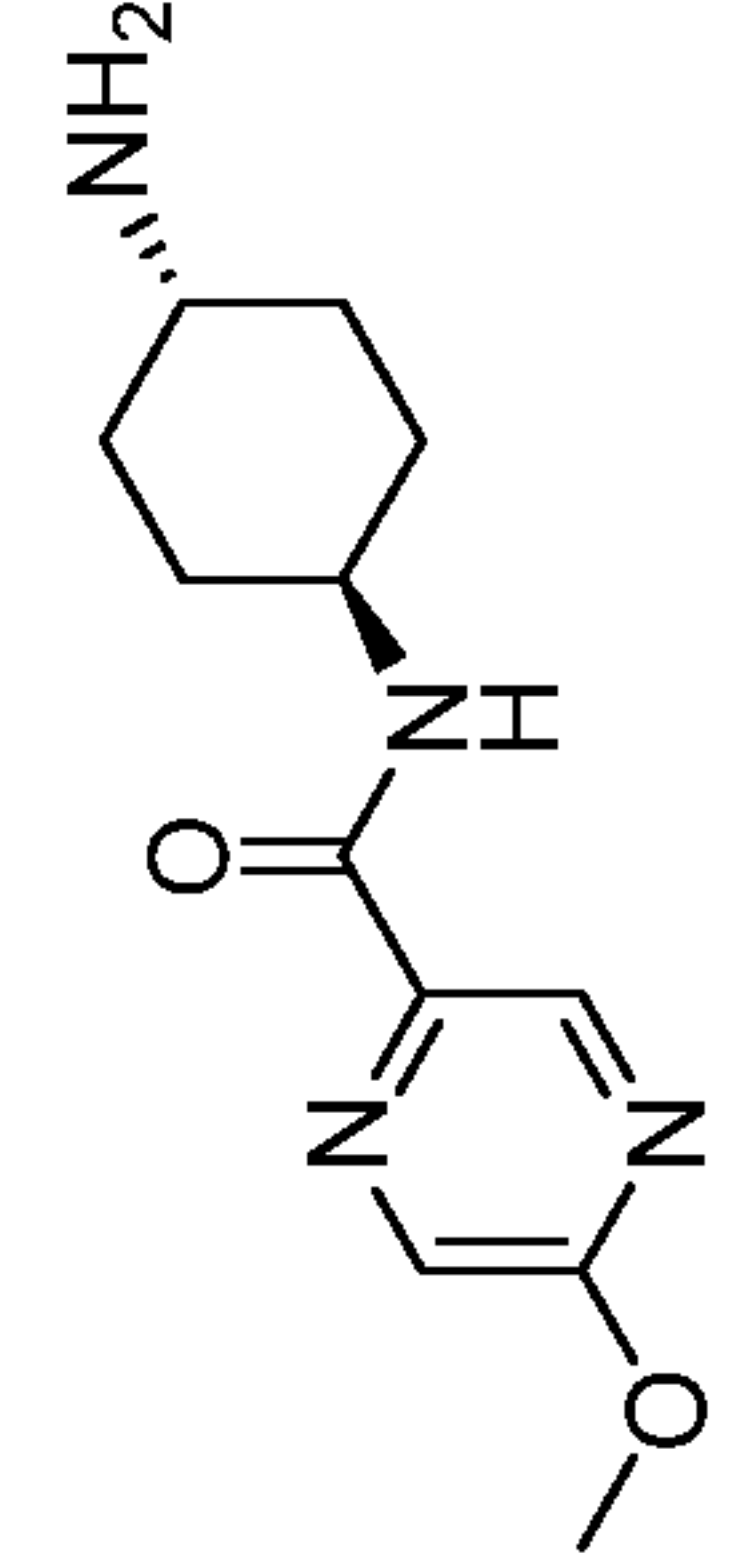
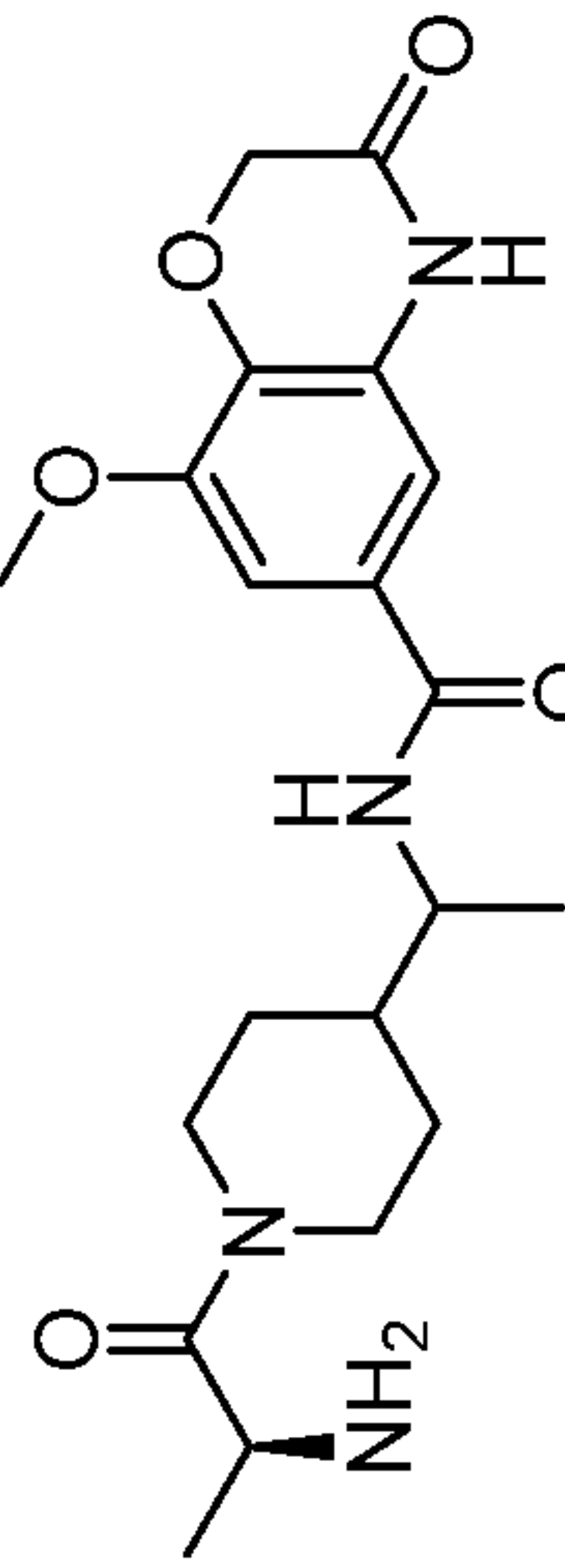
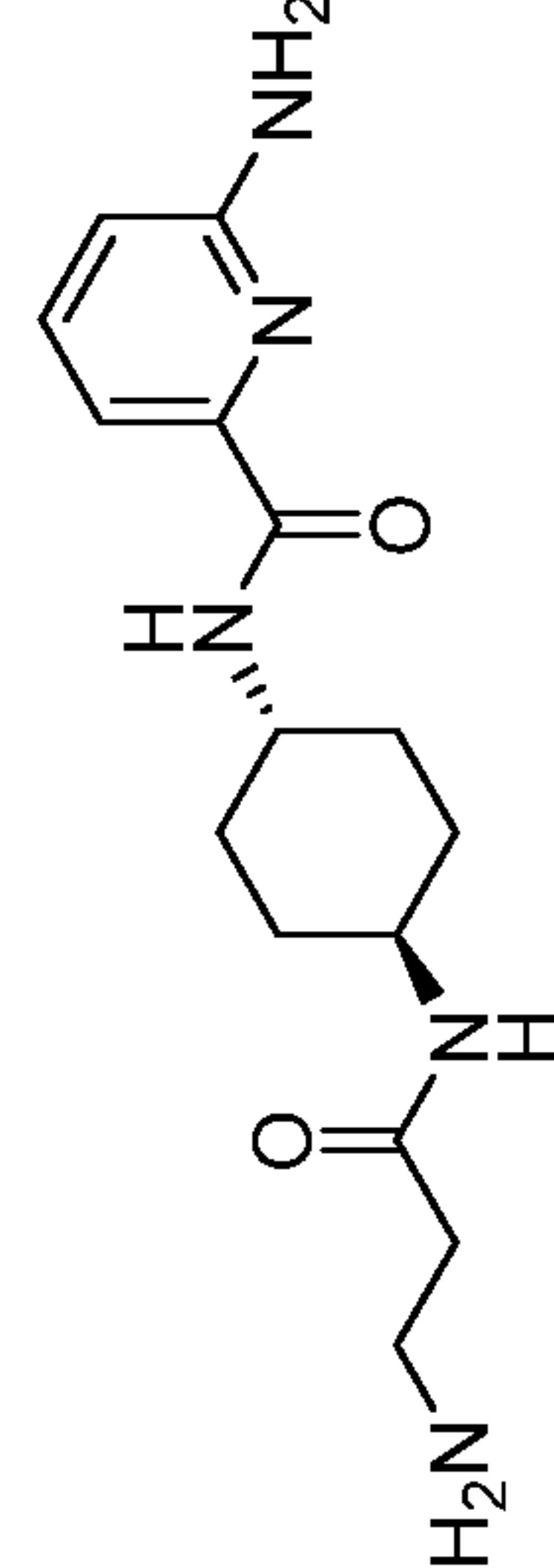
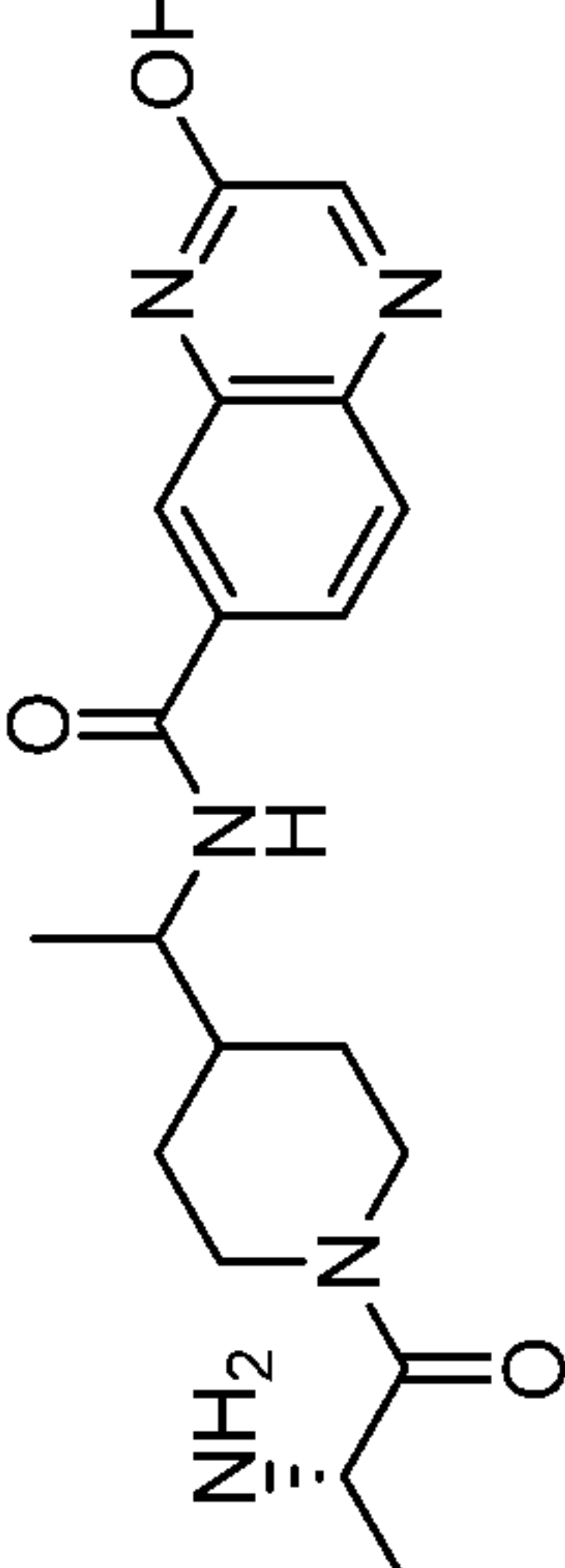
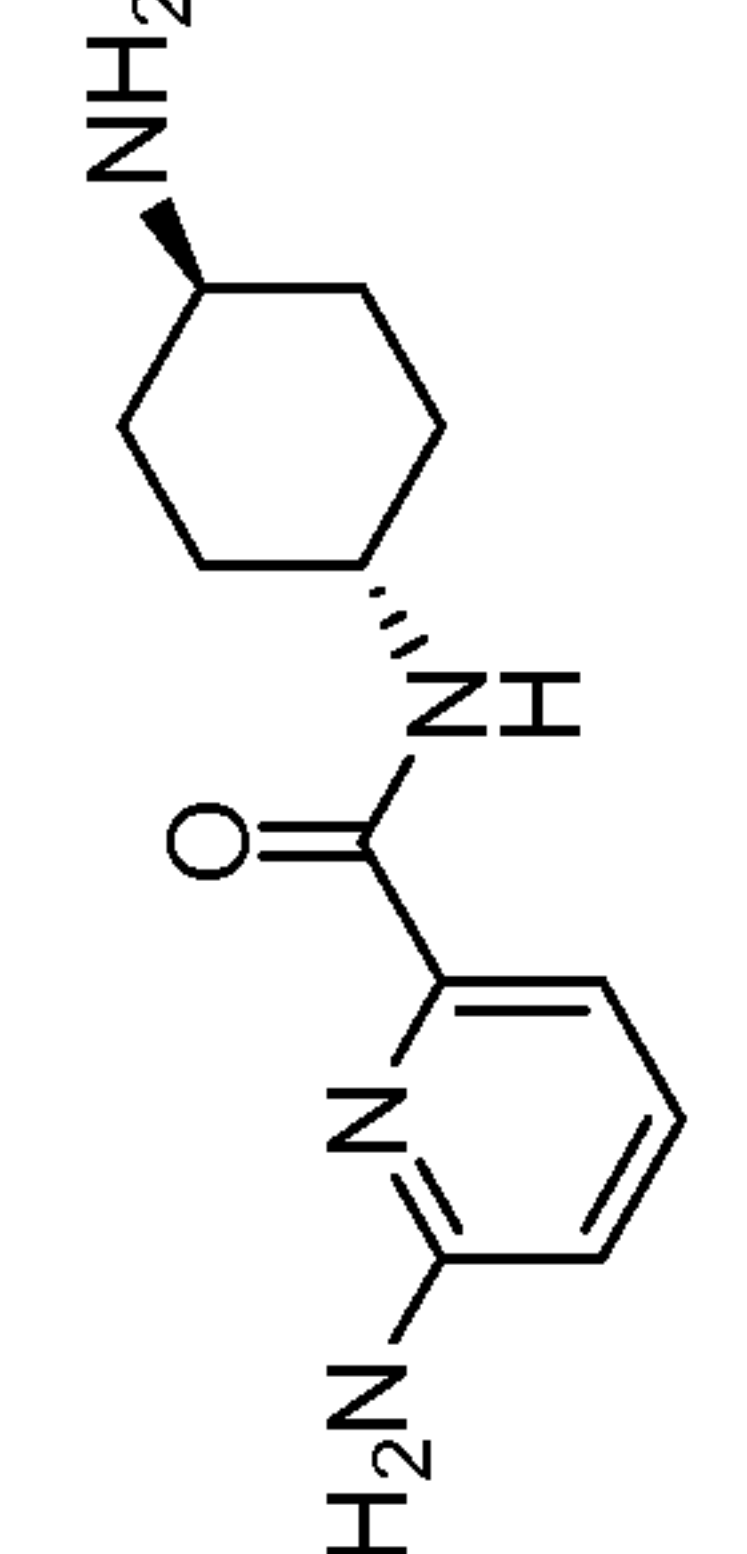
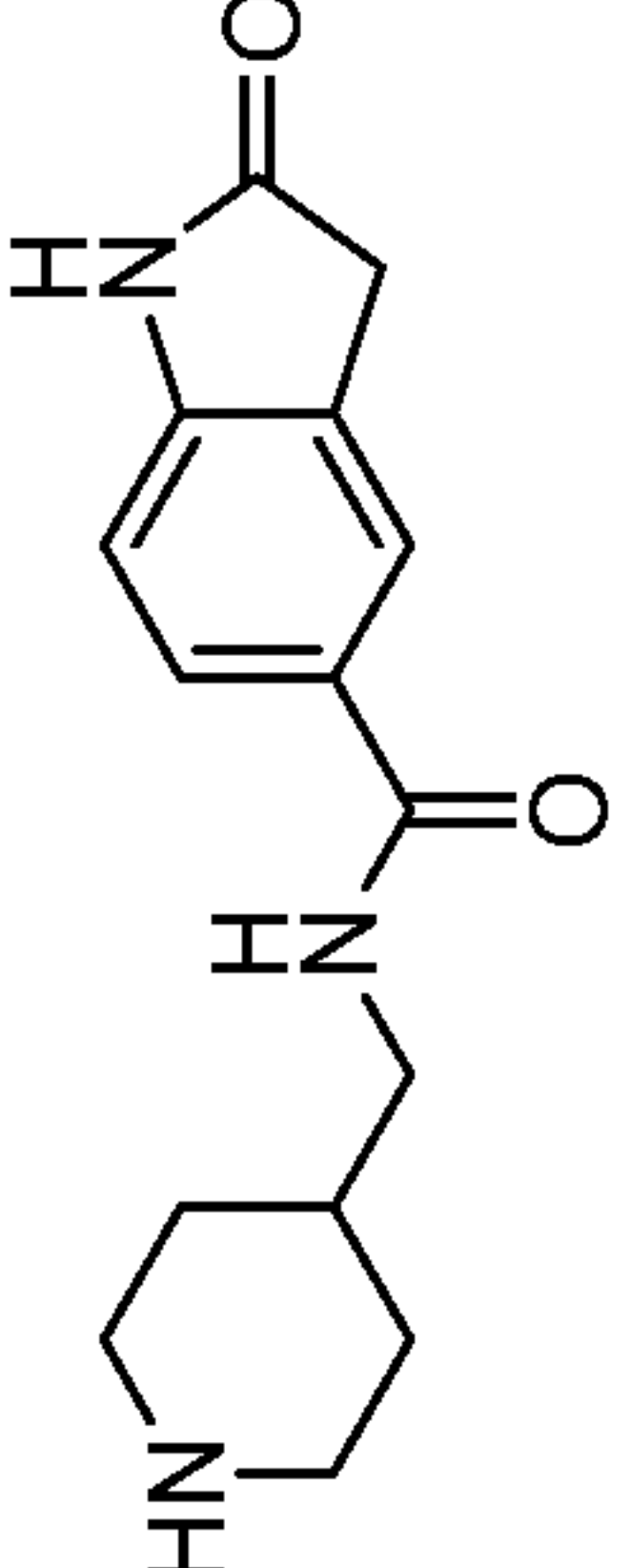
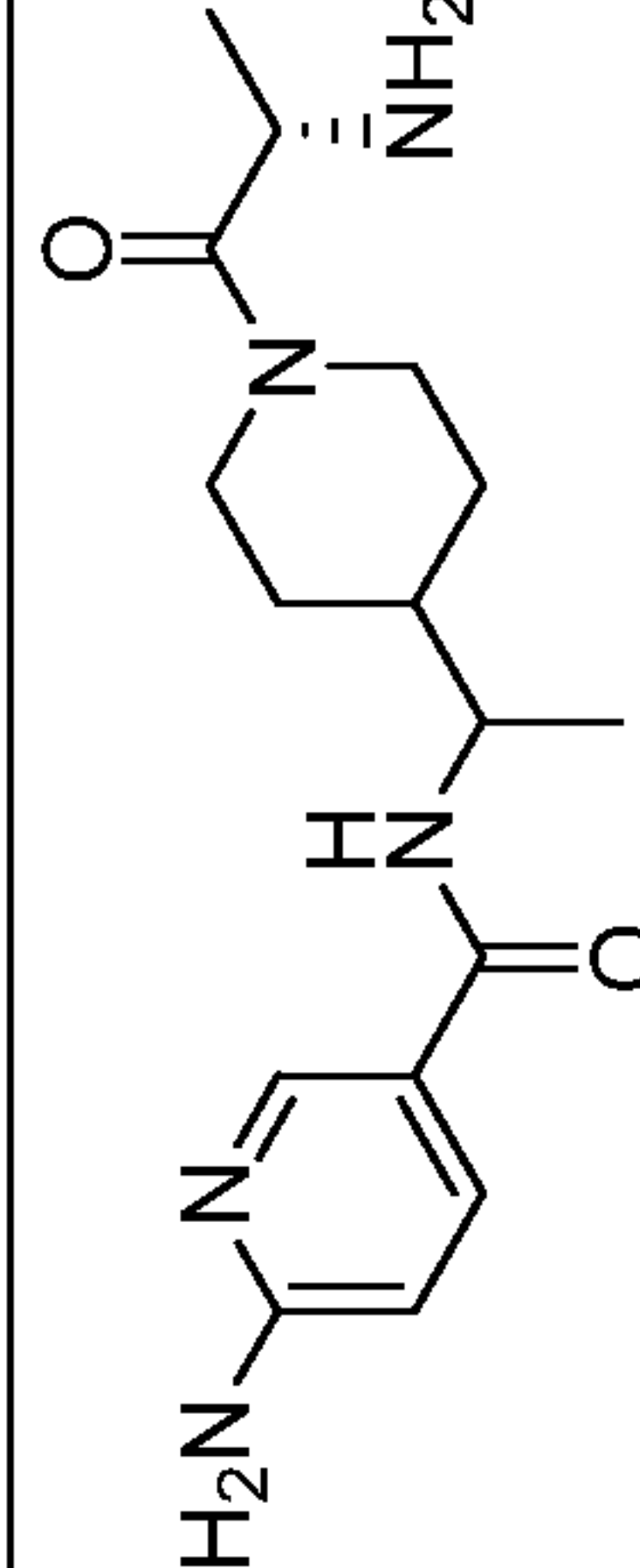
71		TFA	357		None
72		TFA	358		TFA
73		HCl	359		TFA
74		HCl	360		None
75		HCl	361		TFA

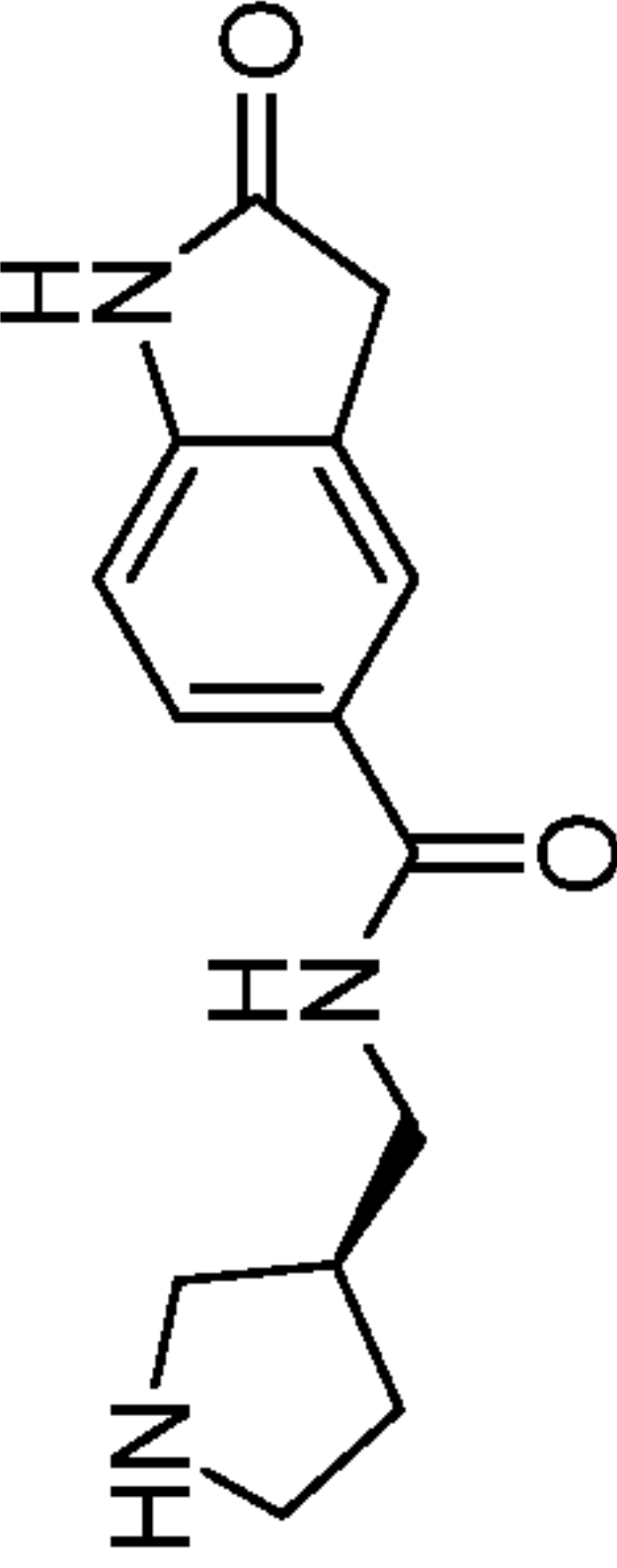
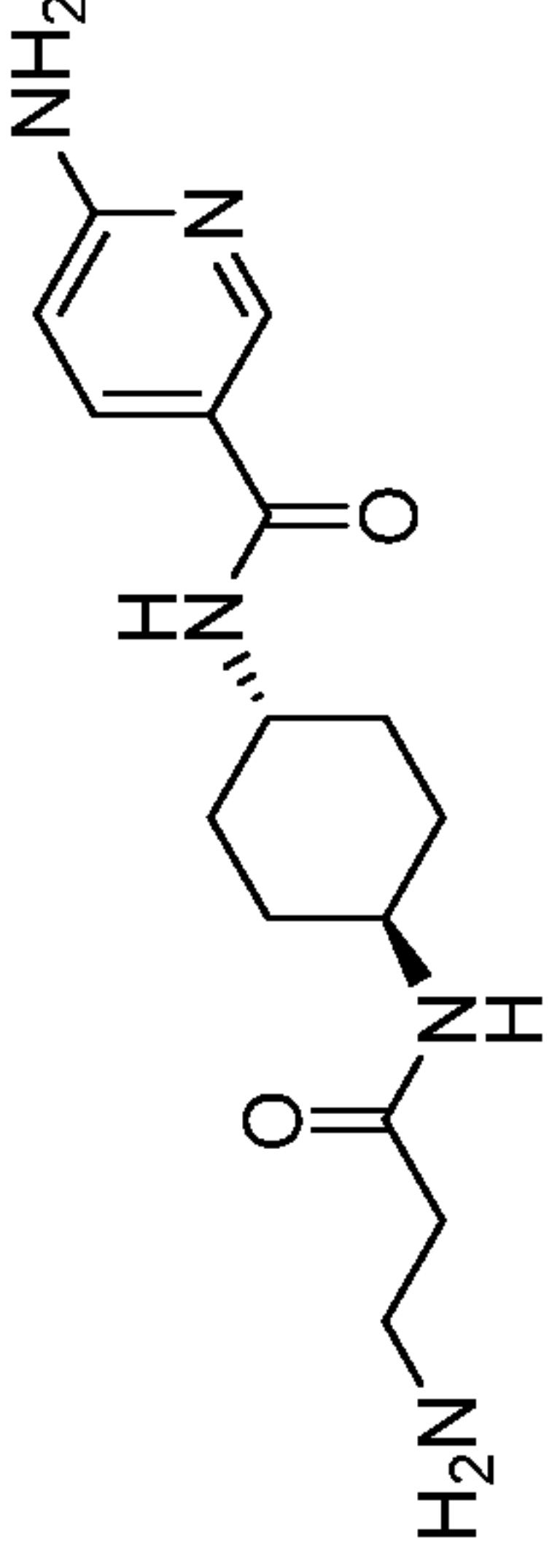
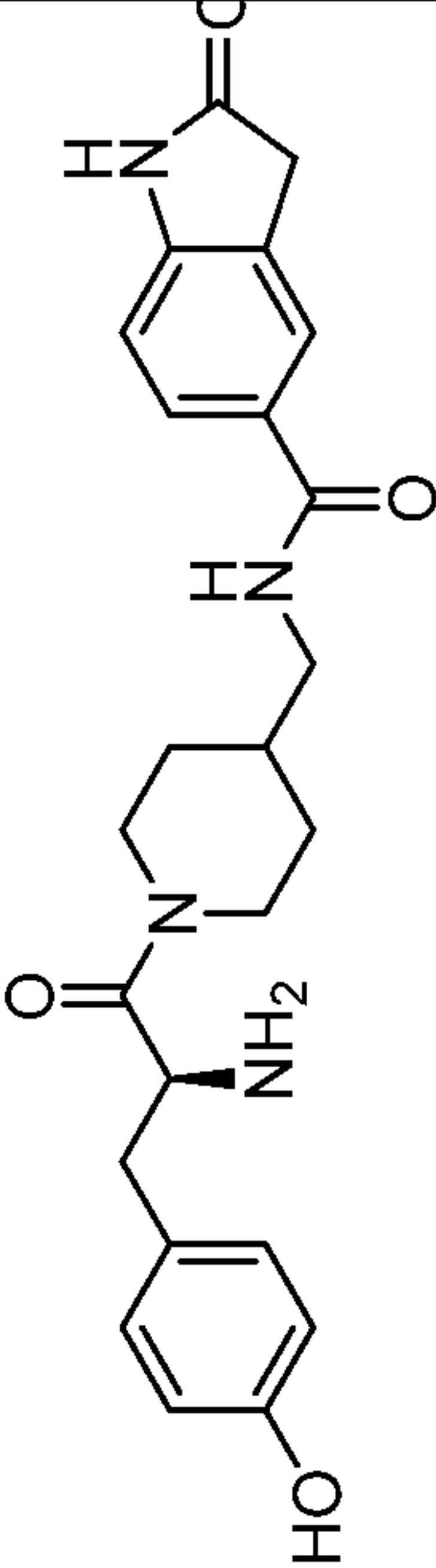
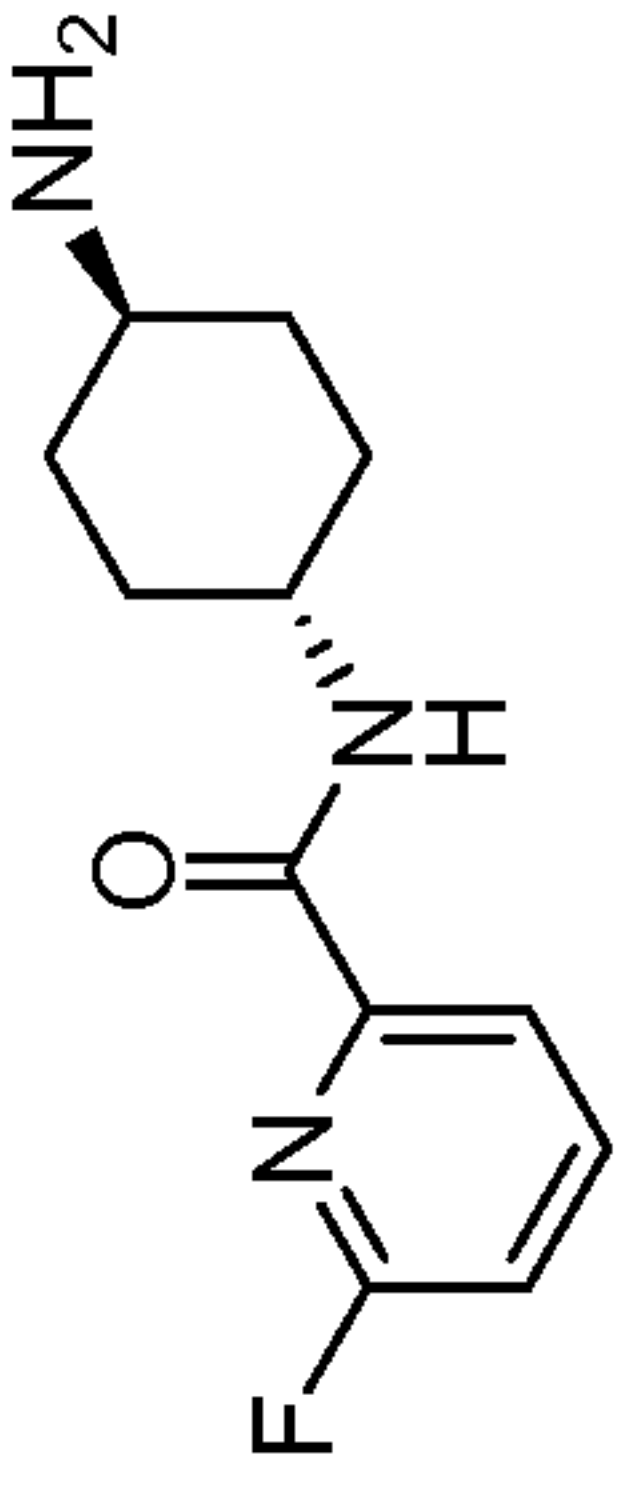
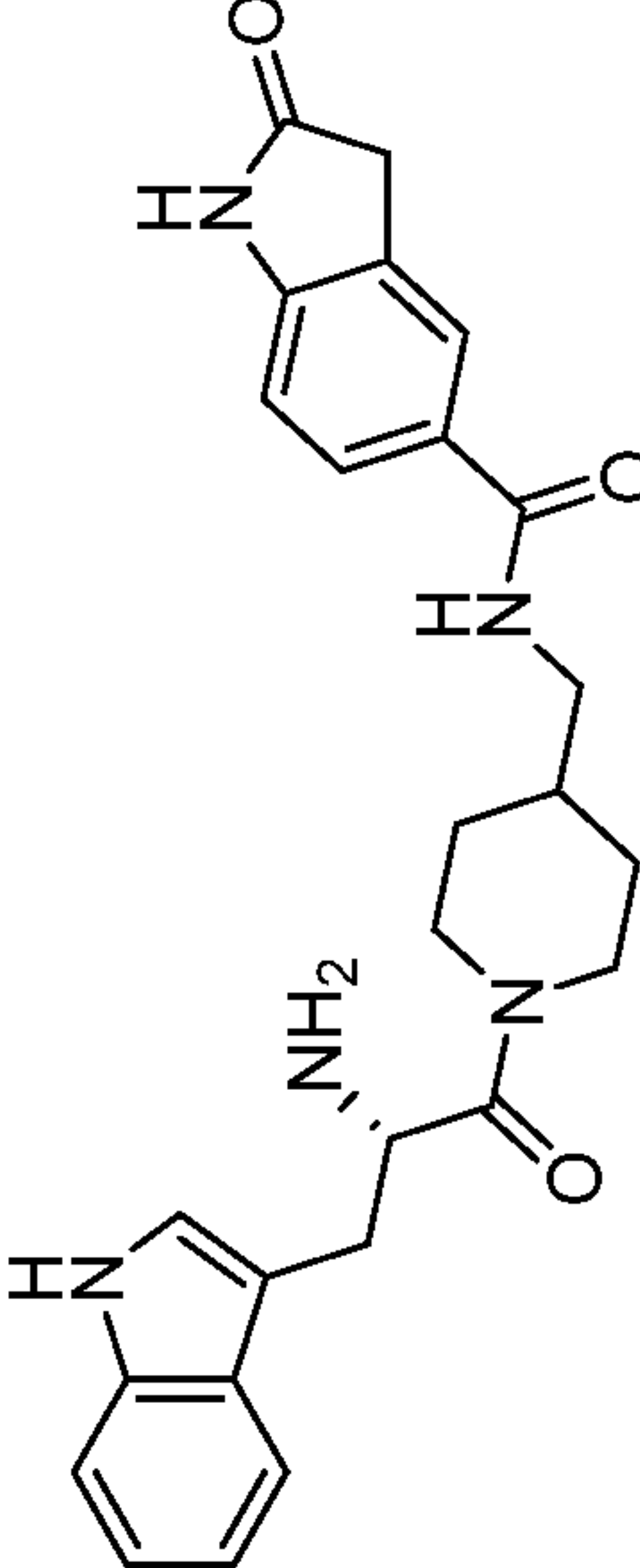
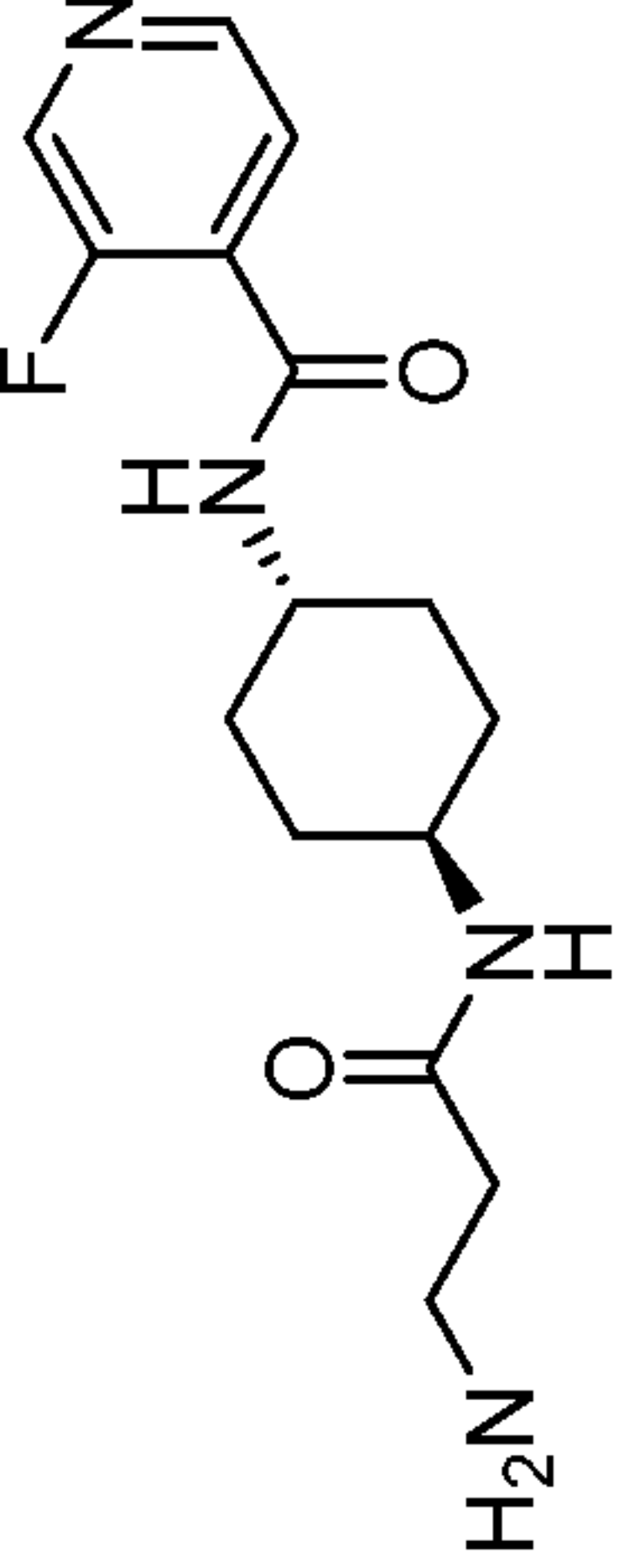
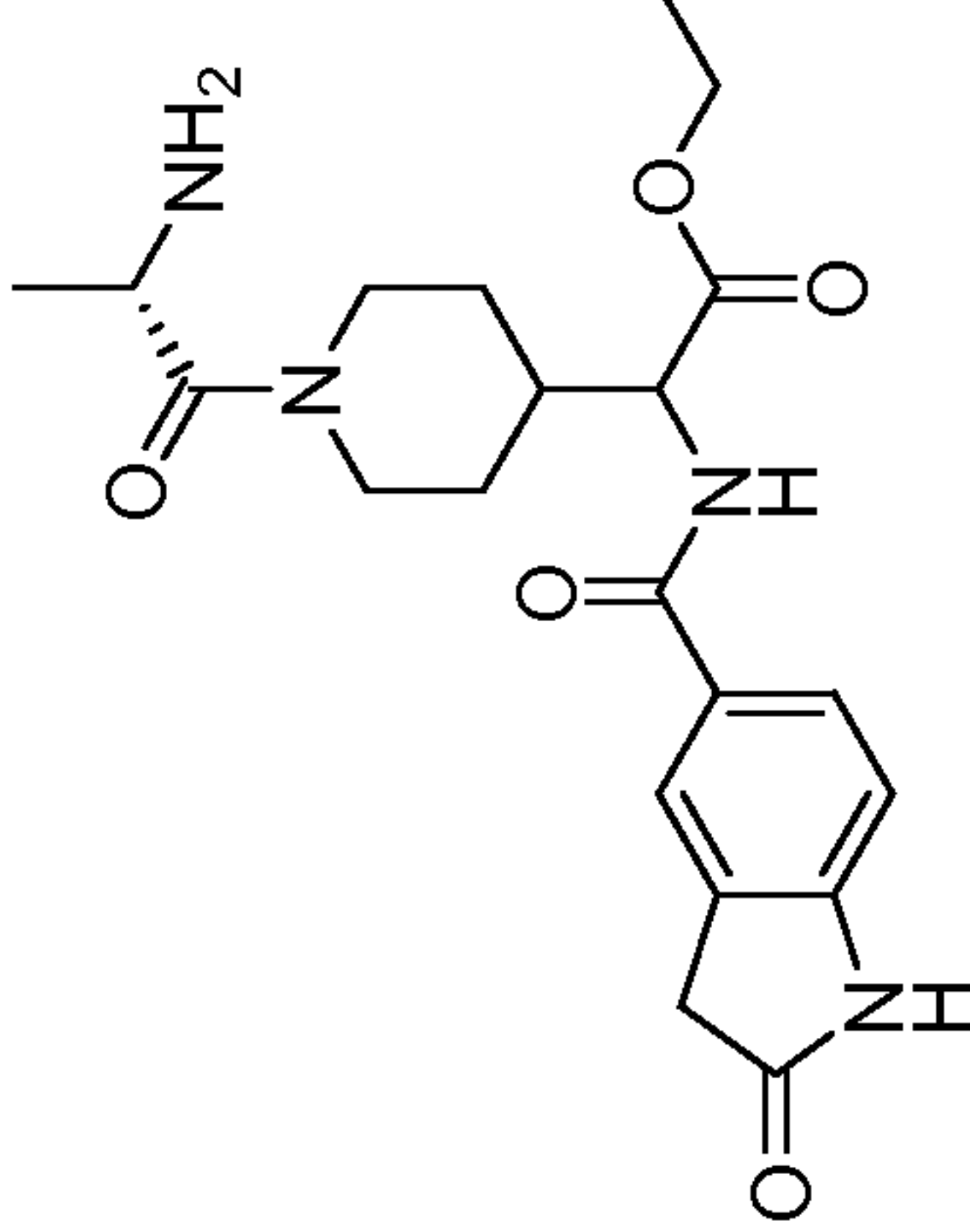
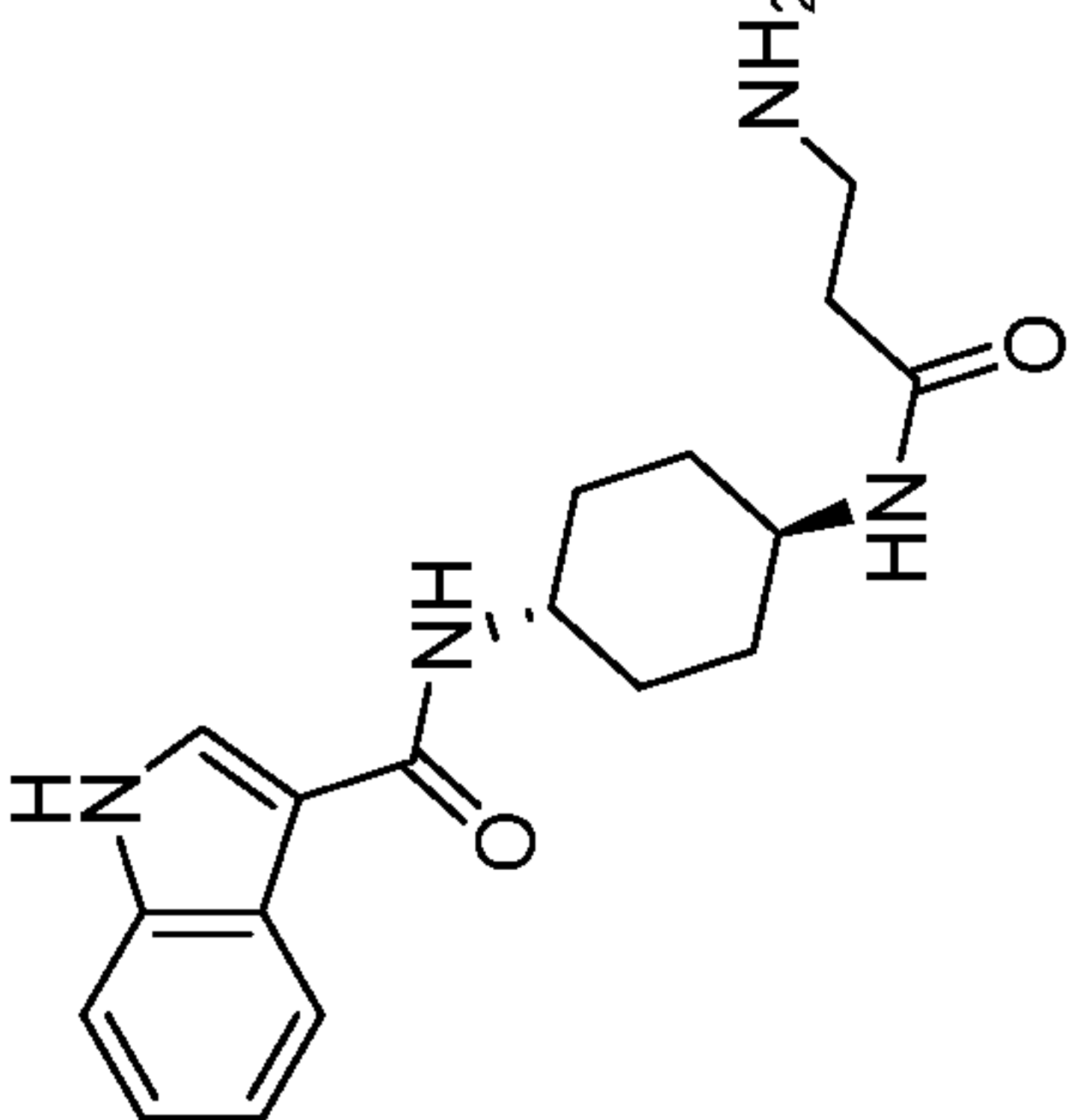
76		HCl	362		TFA
77		HCl	363		TFA
78		HCl	364		TFA
79		HCl	365		TFA
80		HCl	366		TFA
81		TFA	367		TFA

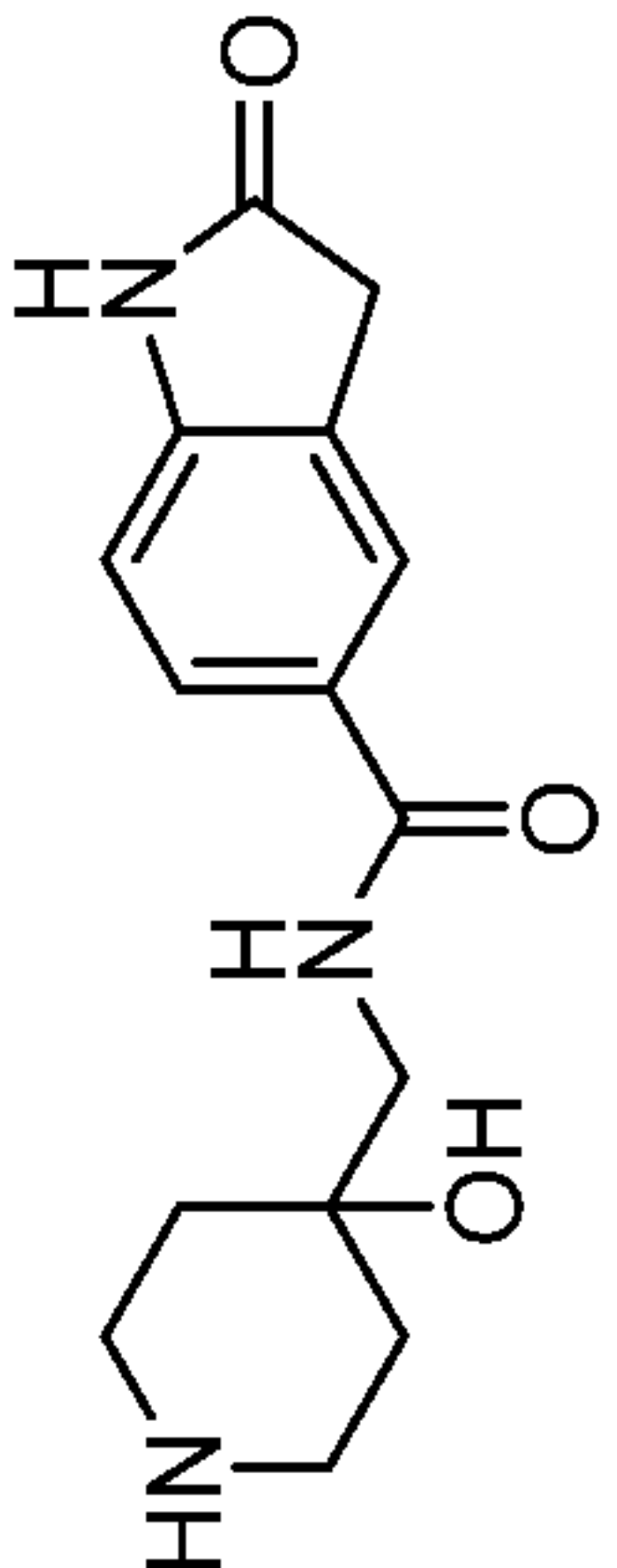
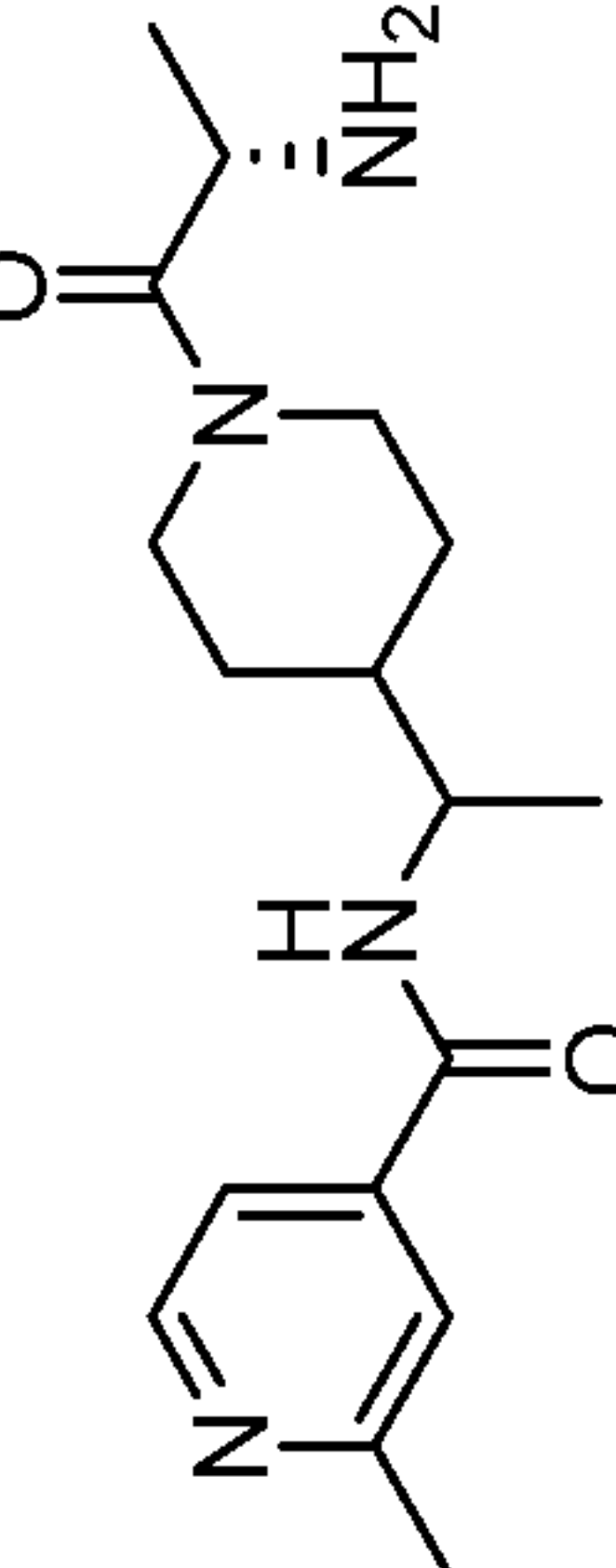
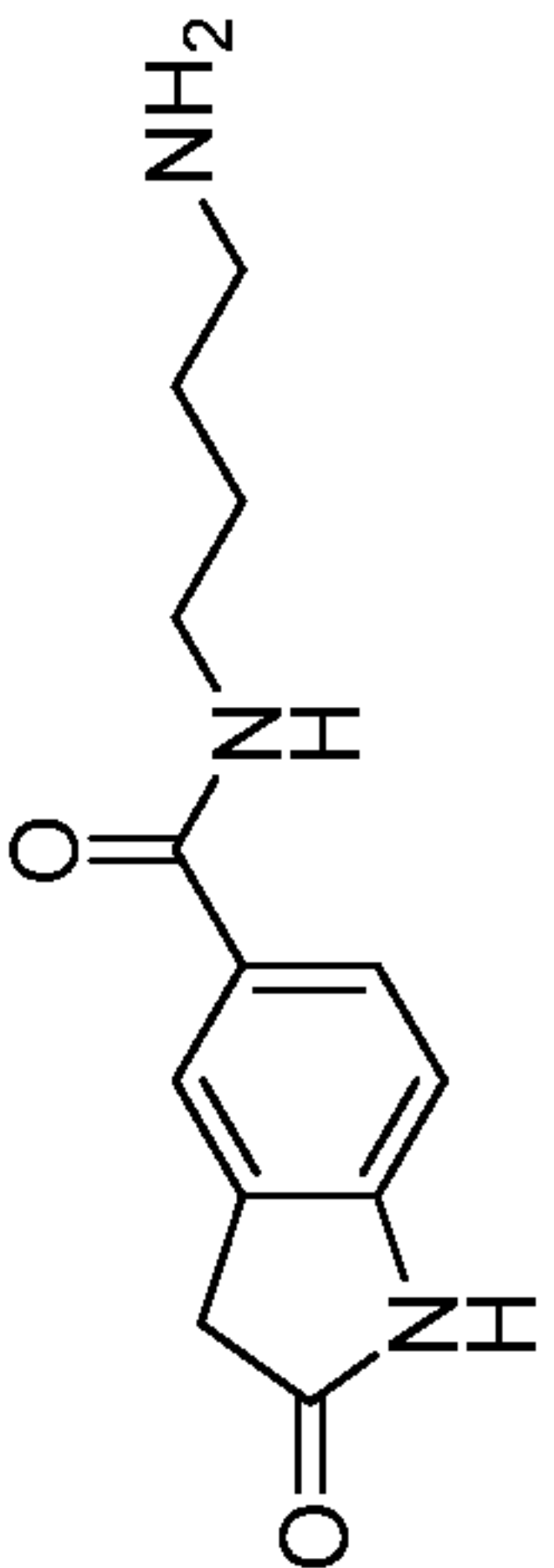
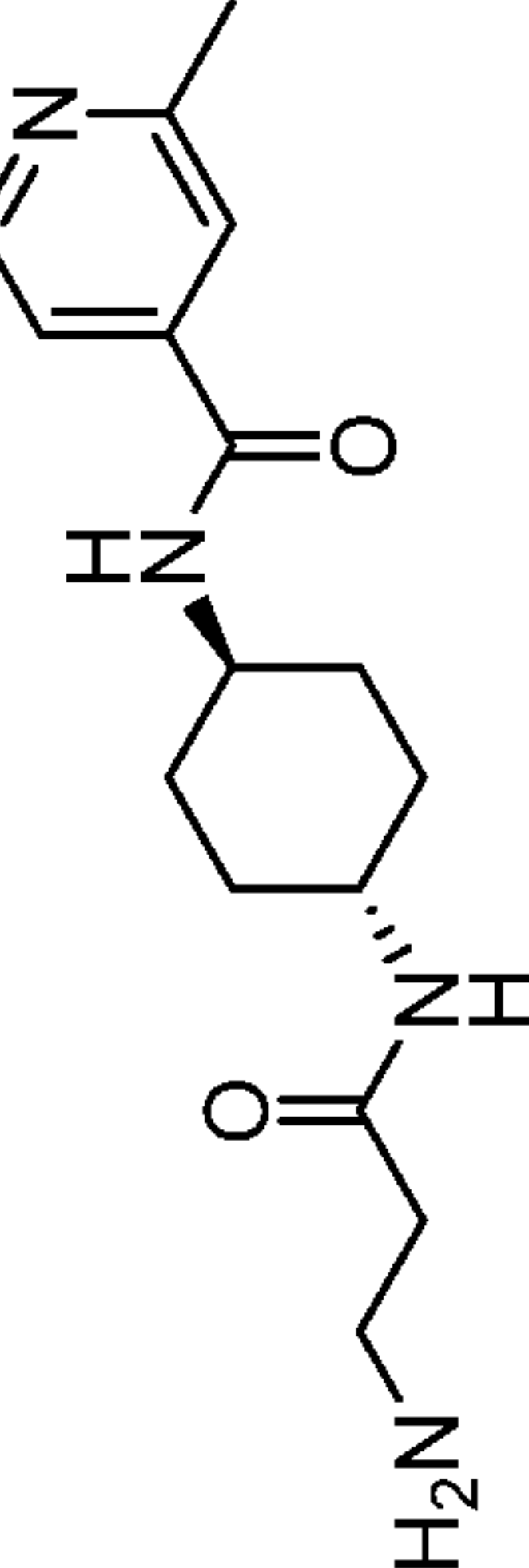
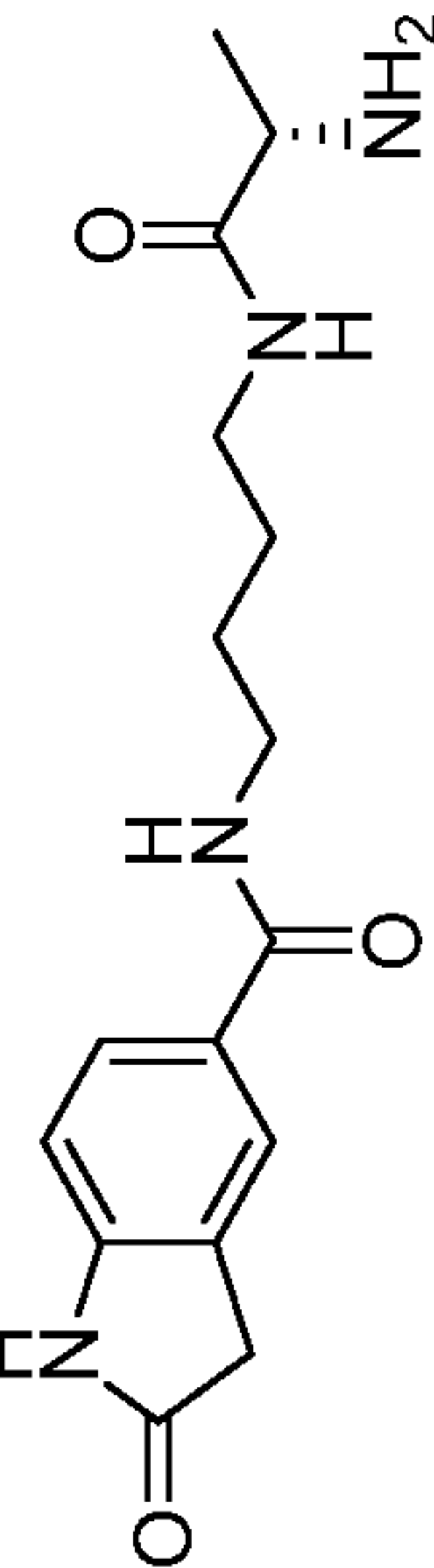
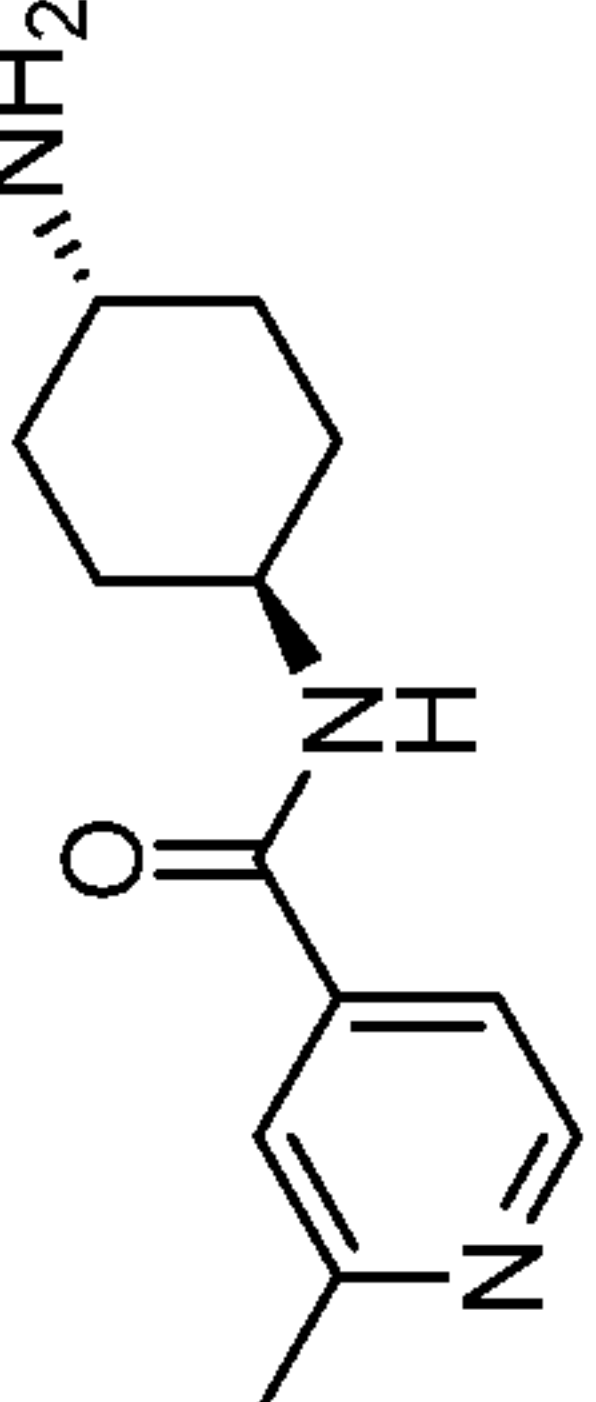
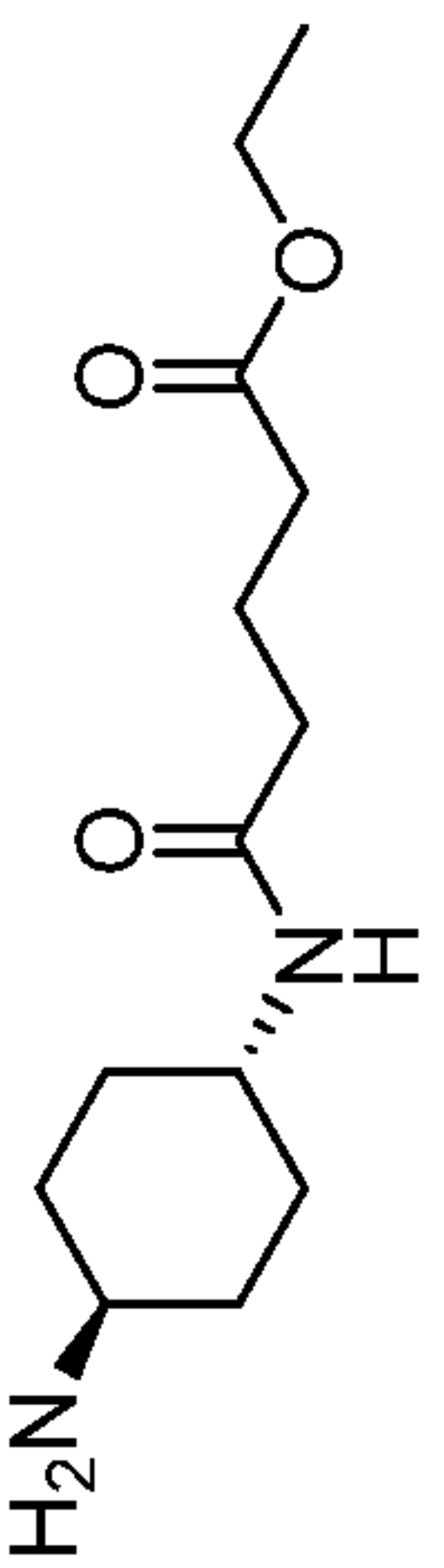
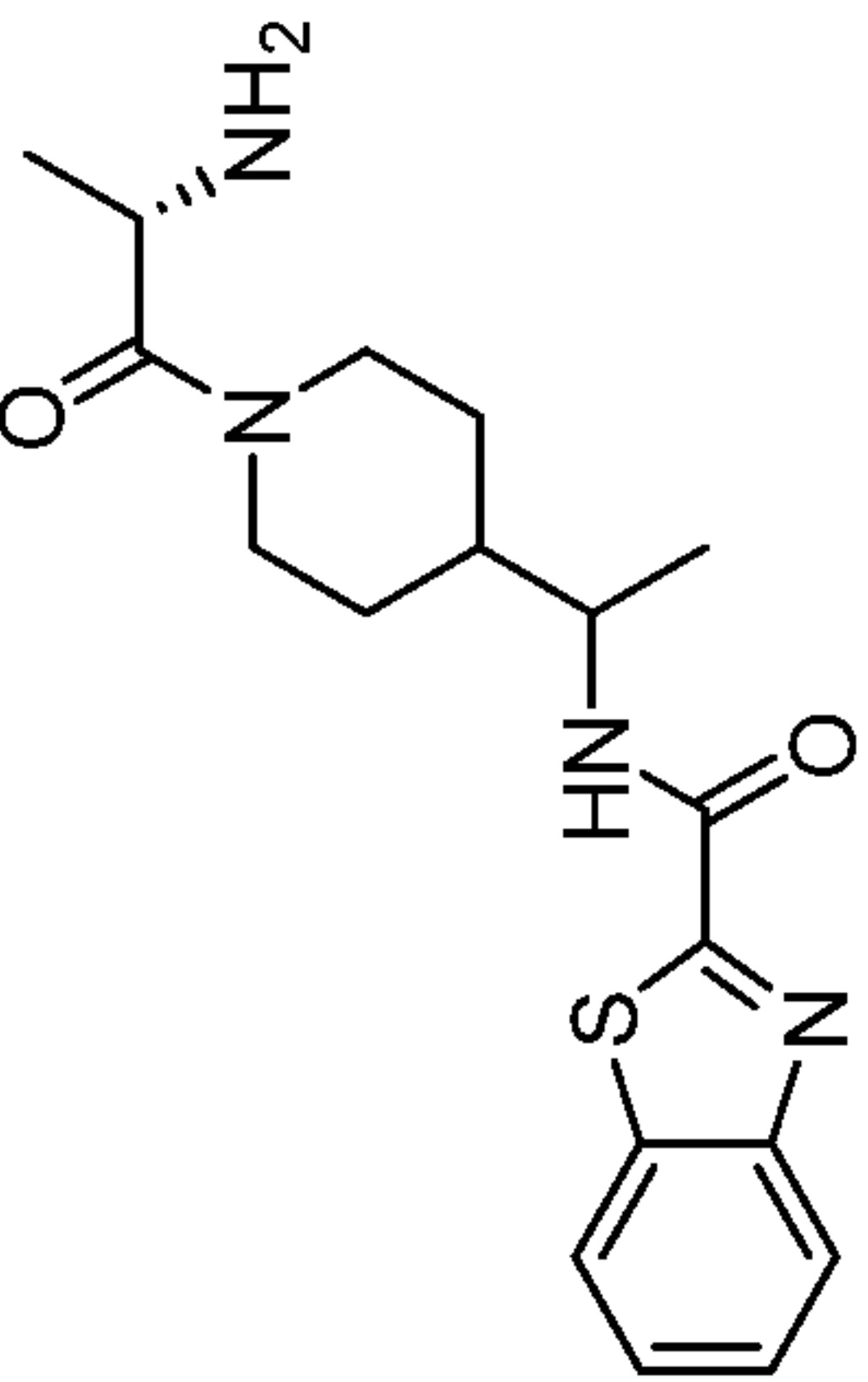
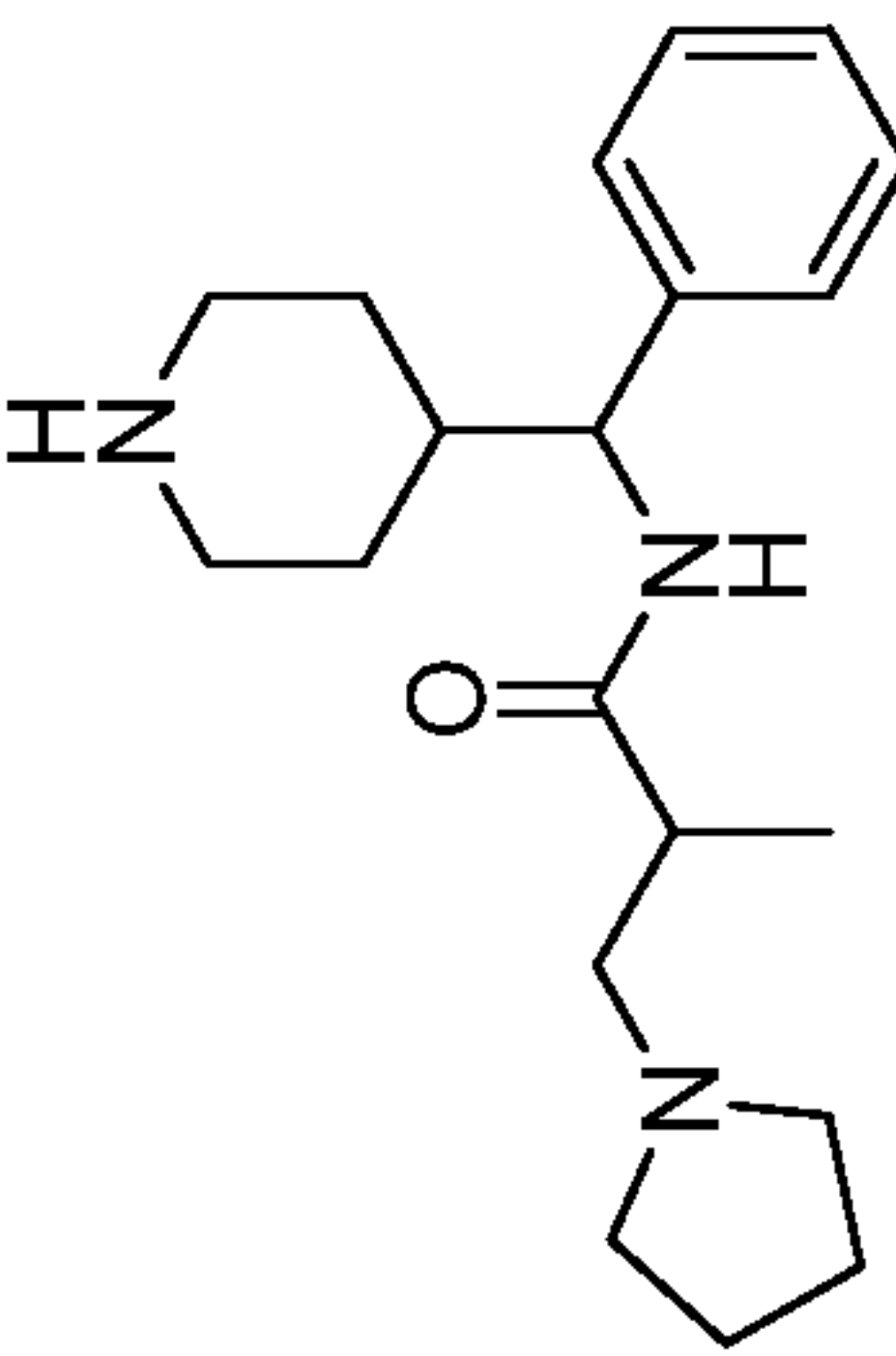
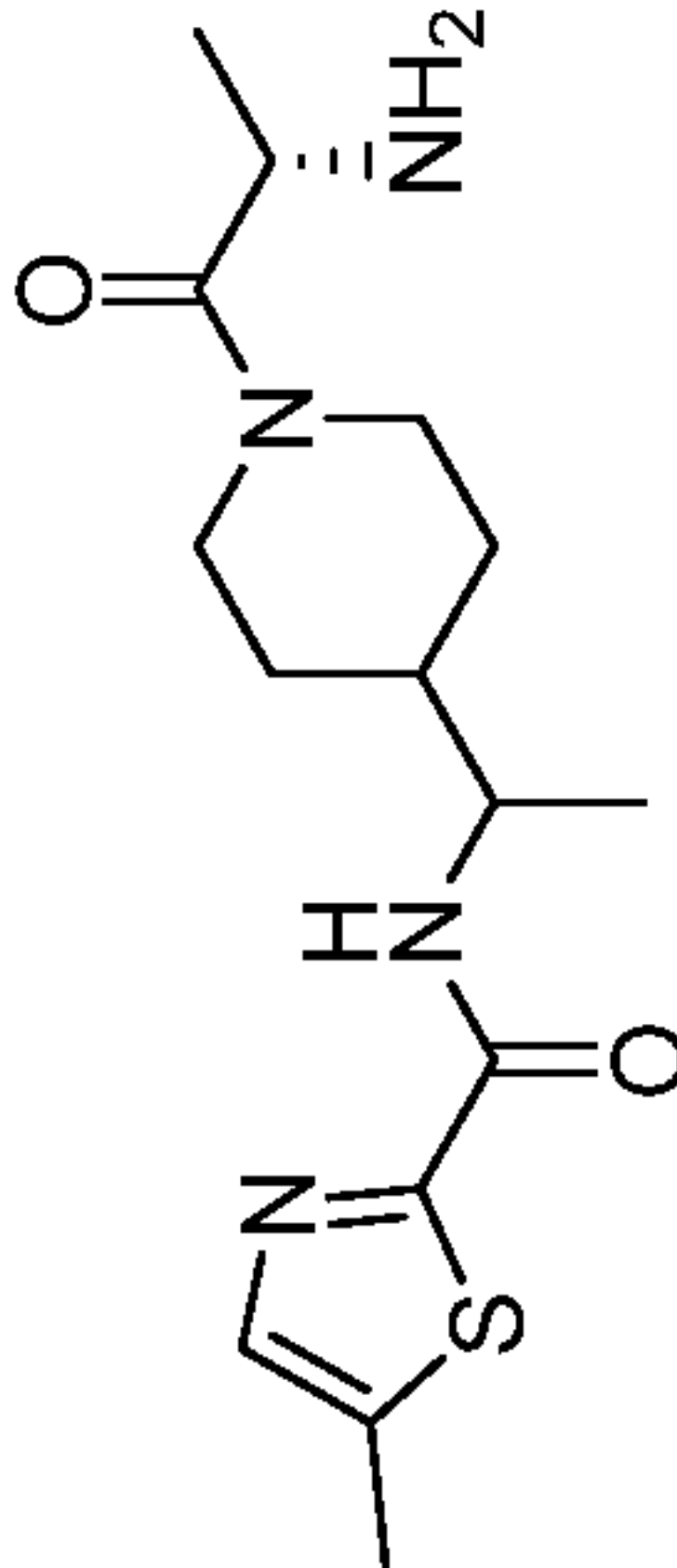
82		TFA	368		HCl
83		TFA	369		HCl
84		TFA	370		TFA
85		HCl	371		TFA

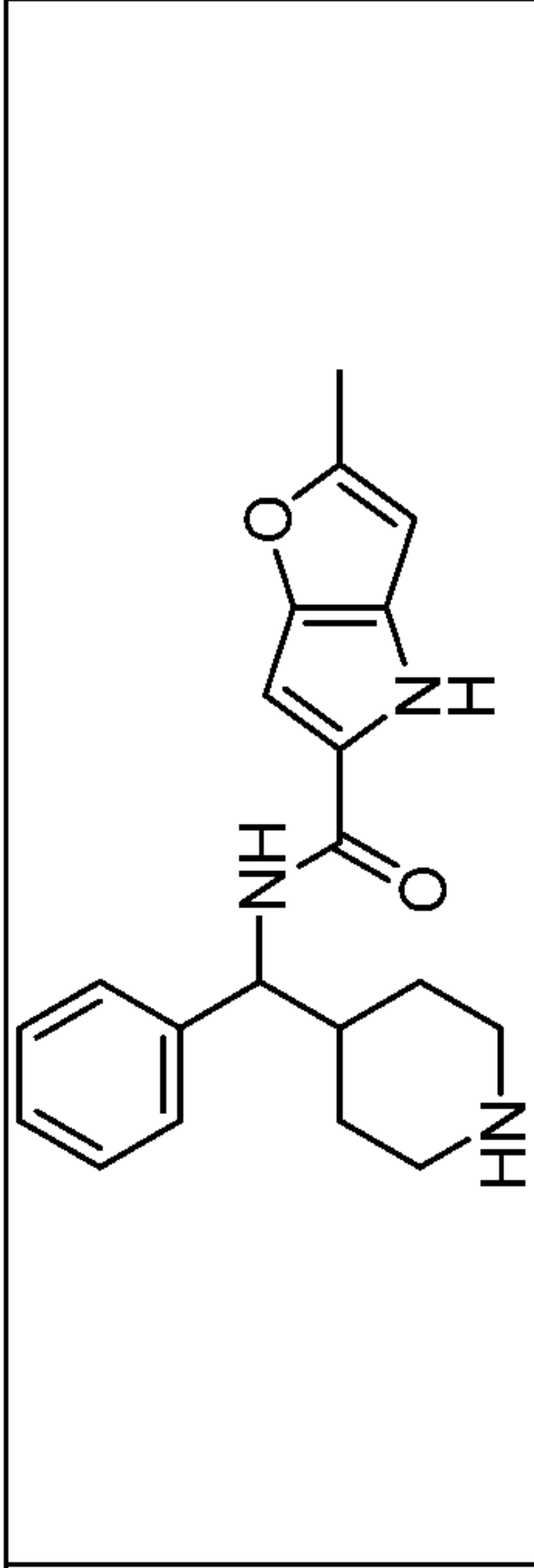
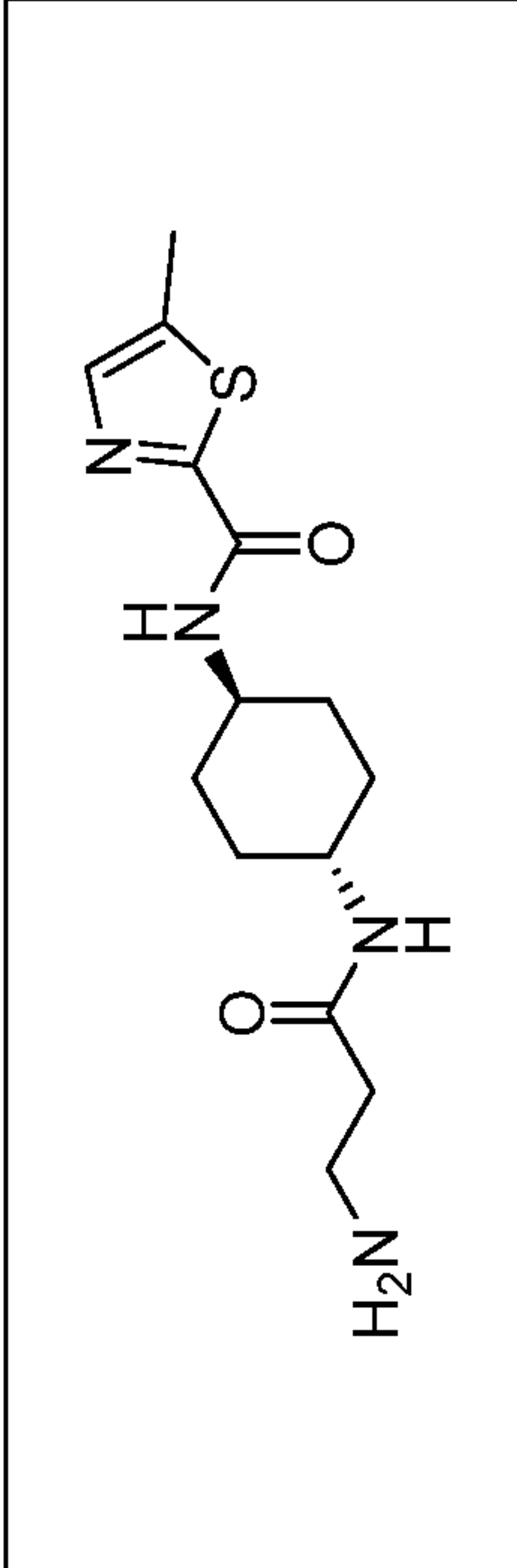
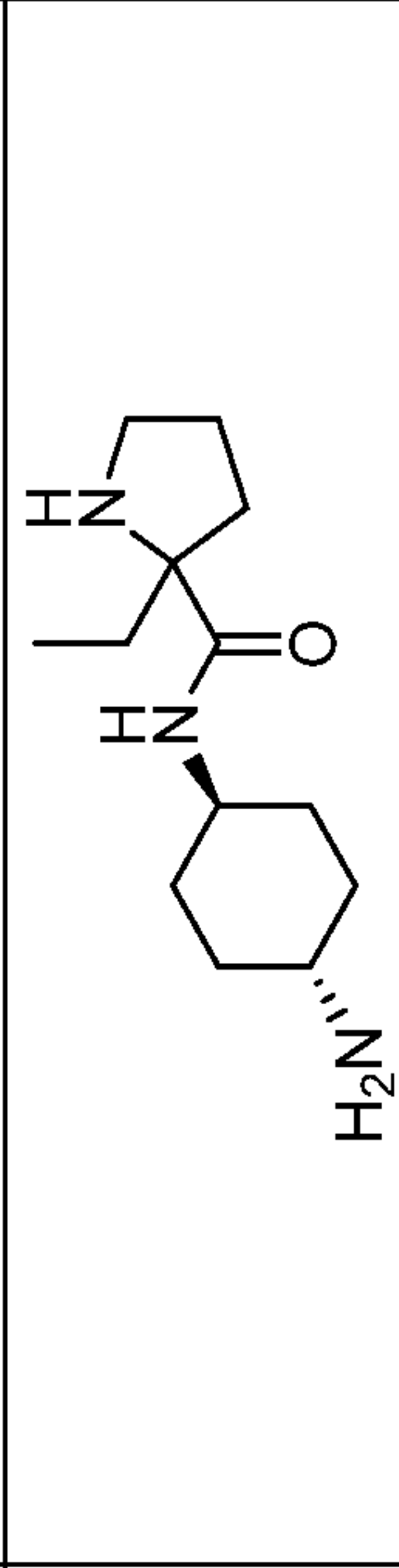
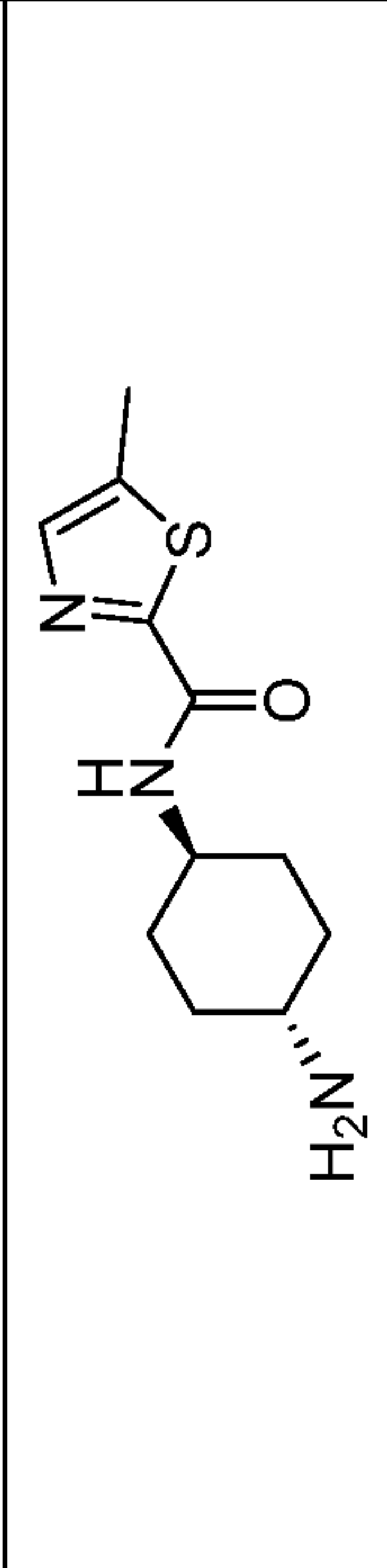
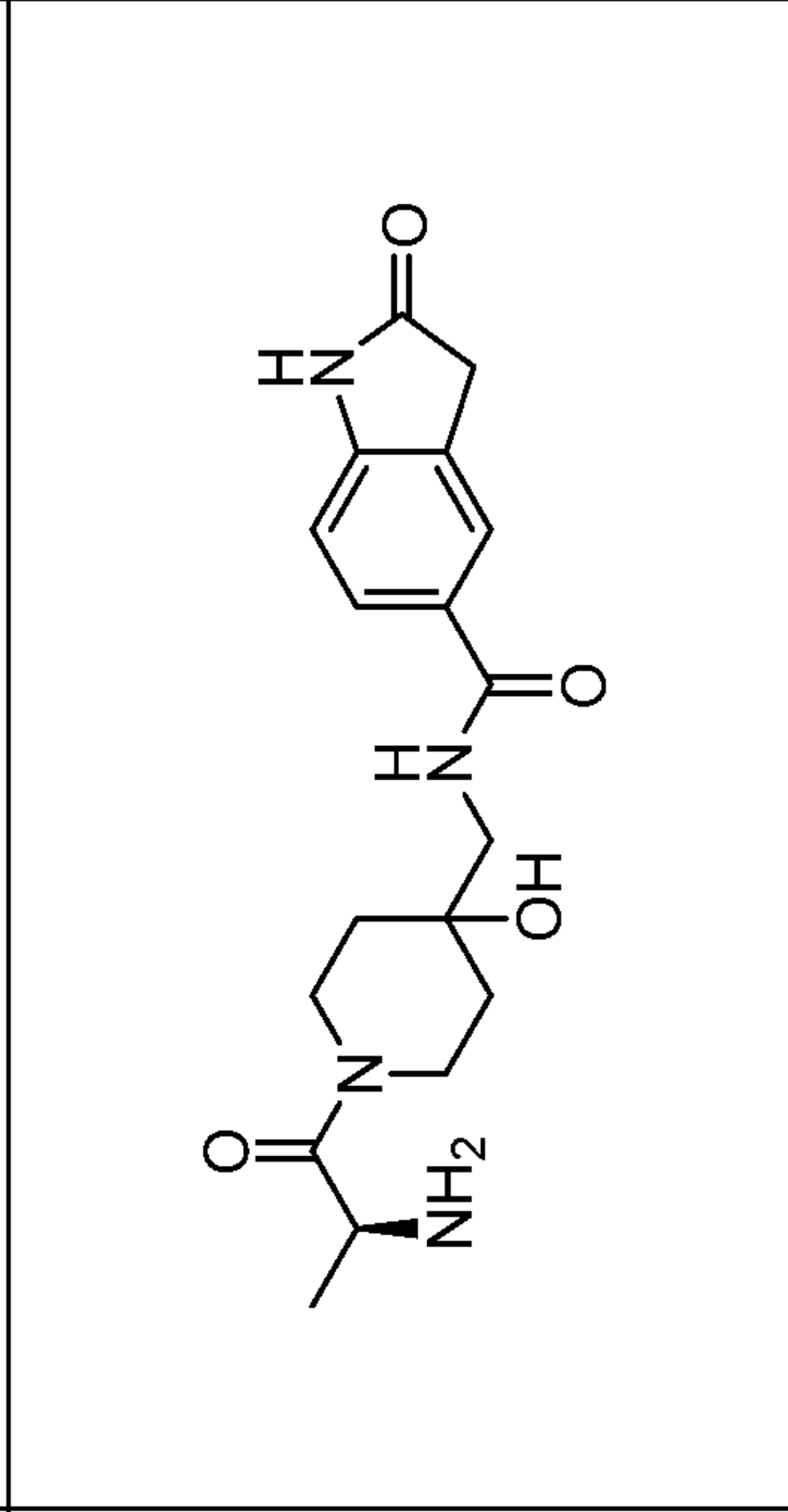
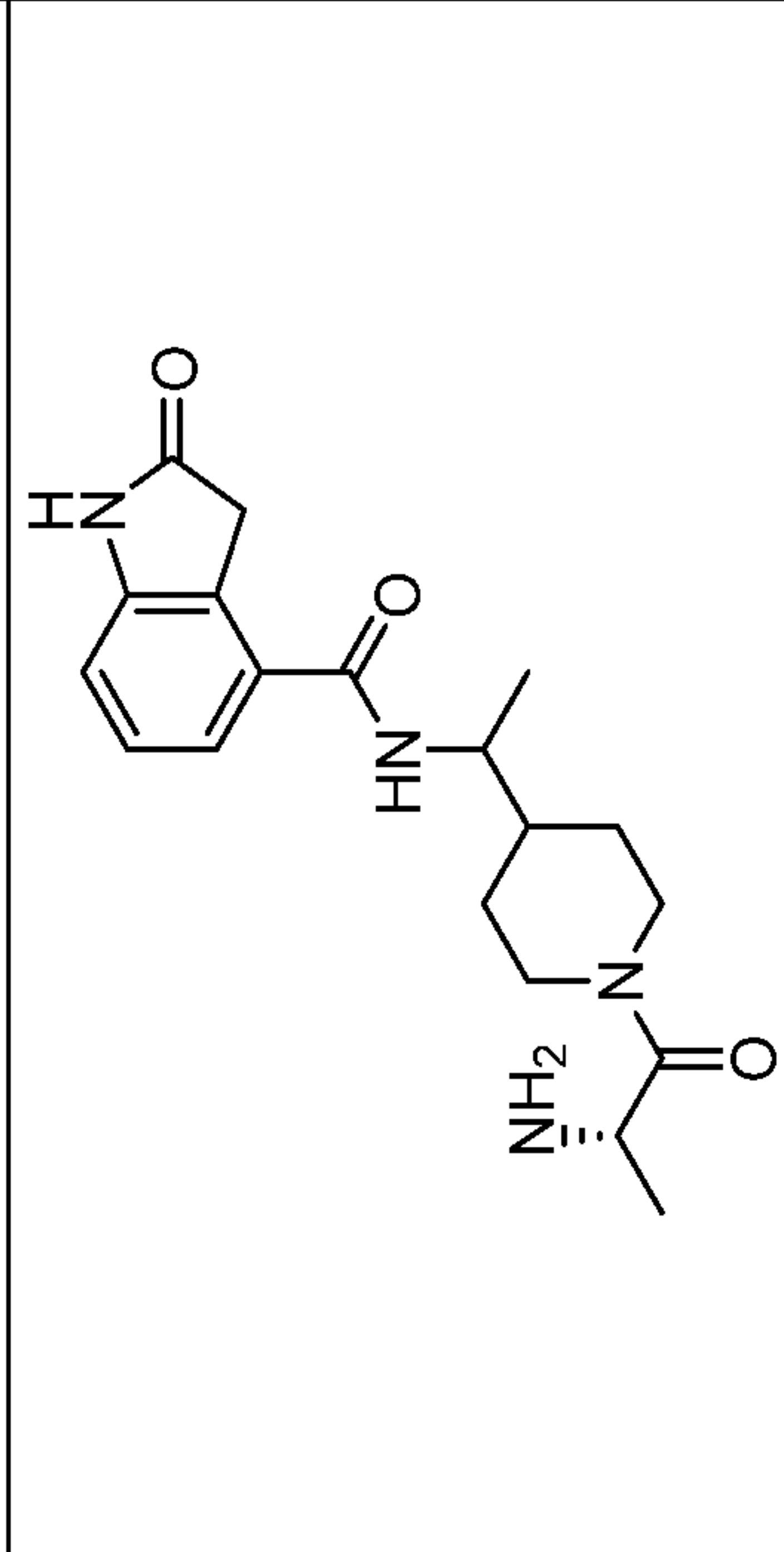
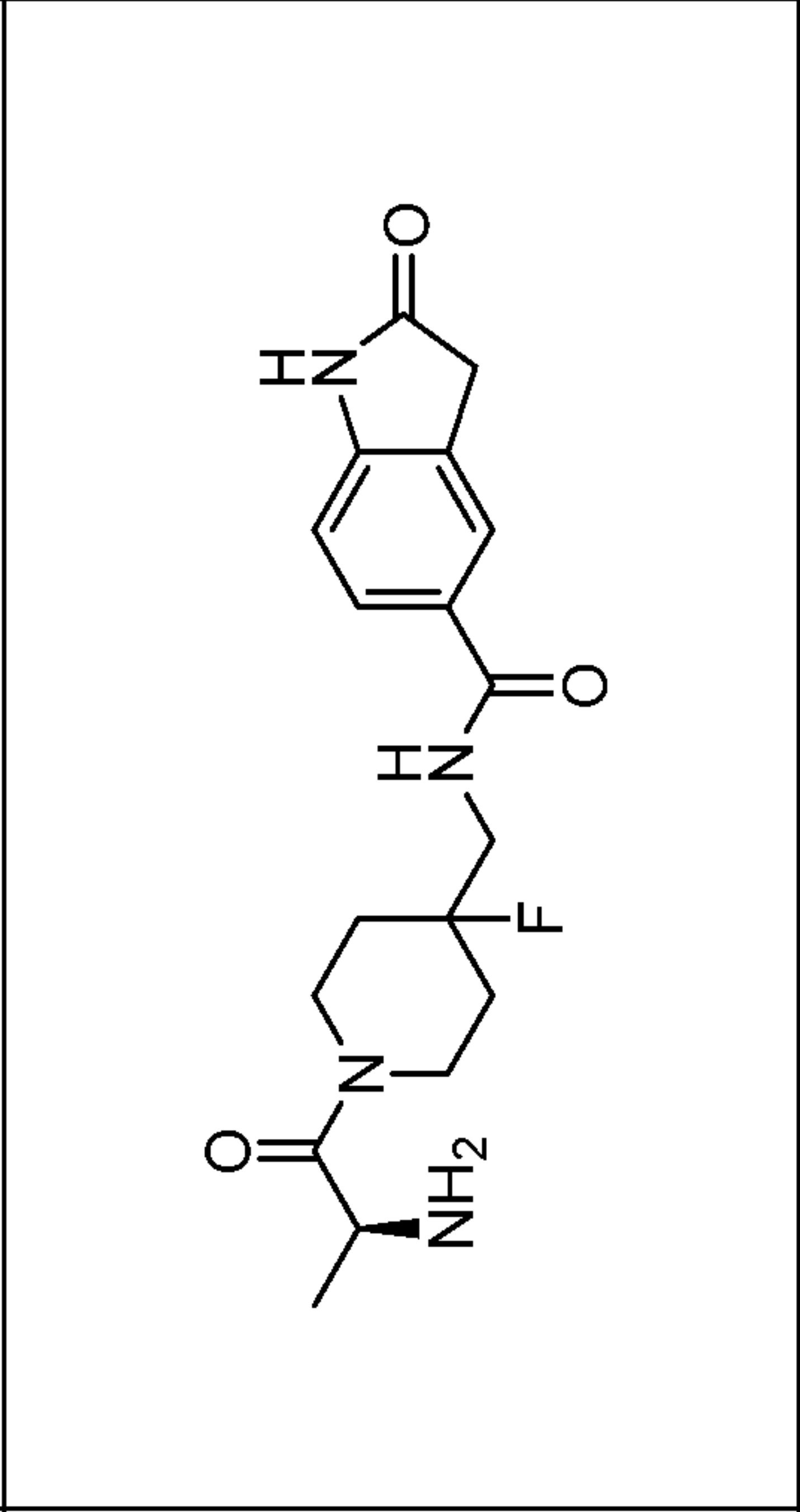
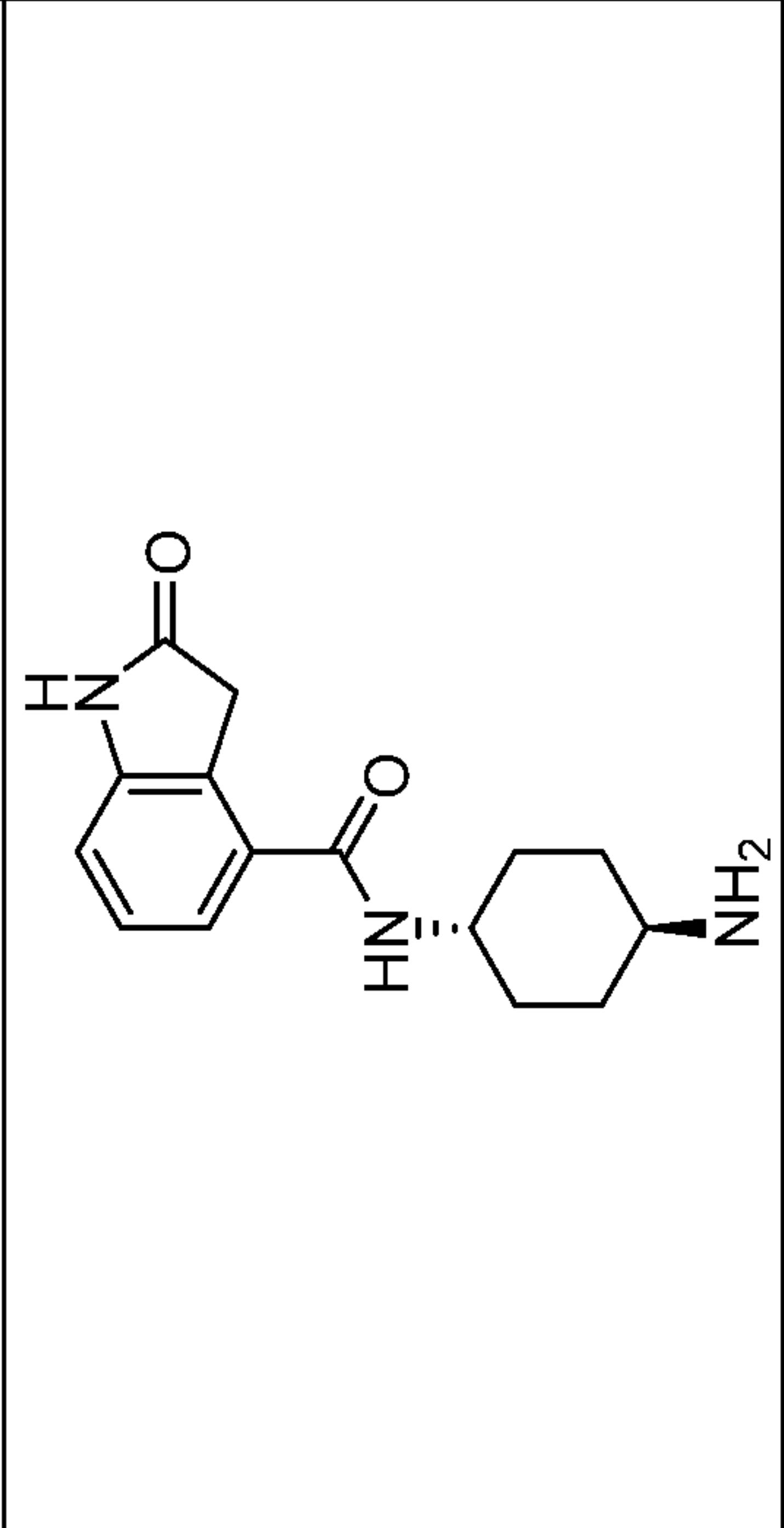
86		HCl	372		TFA
87		HCl	373		TFA
88		TFA	374		TFA
89		TFA	375		TFA
90		TFA	376		TFA

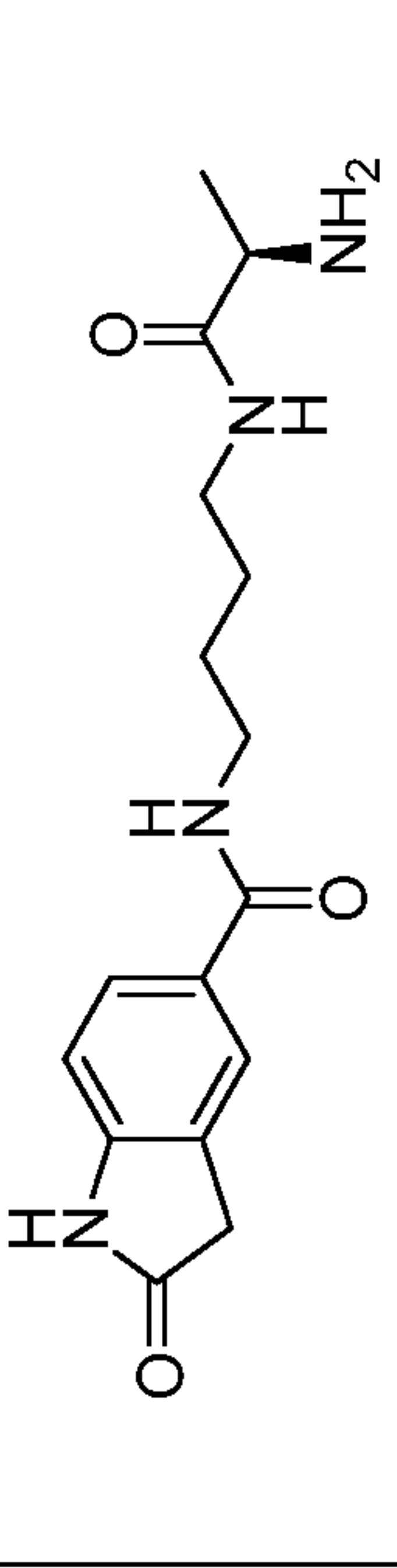
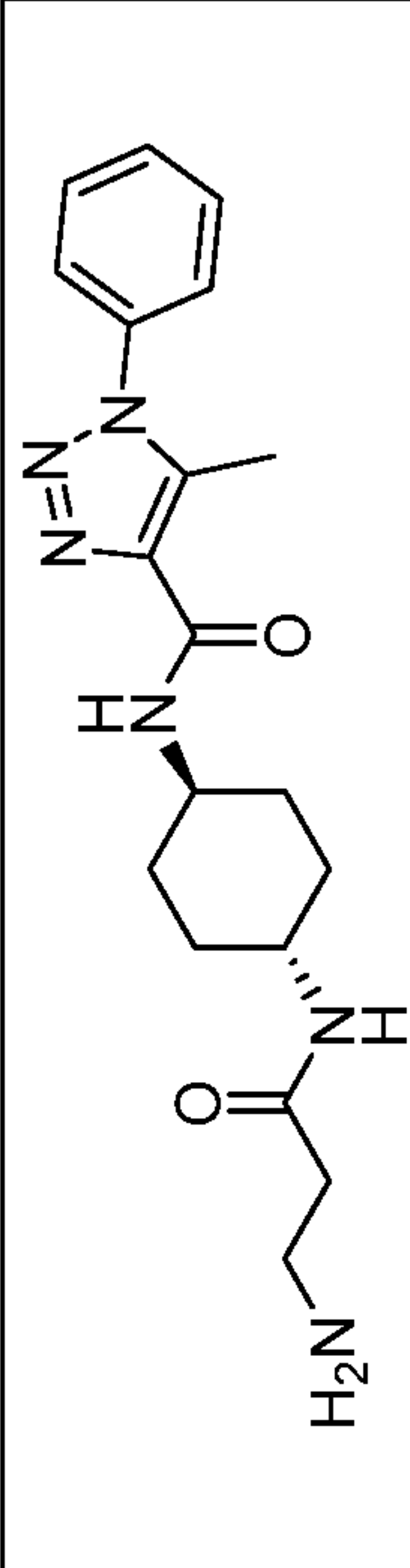
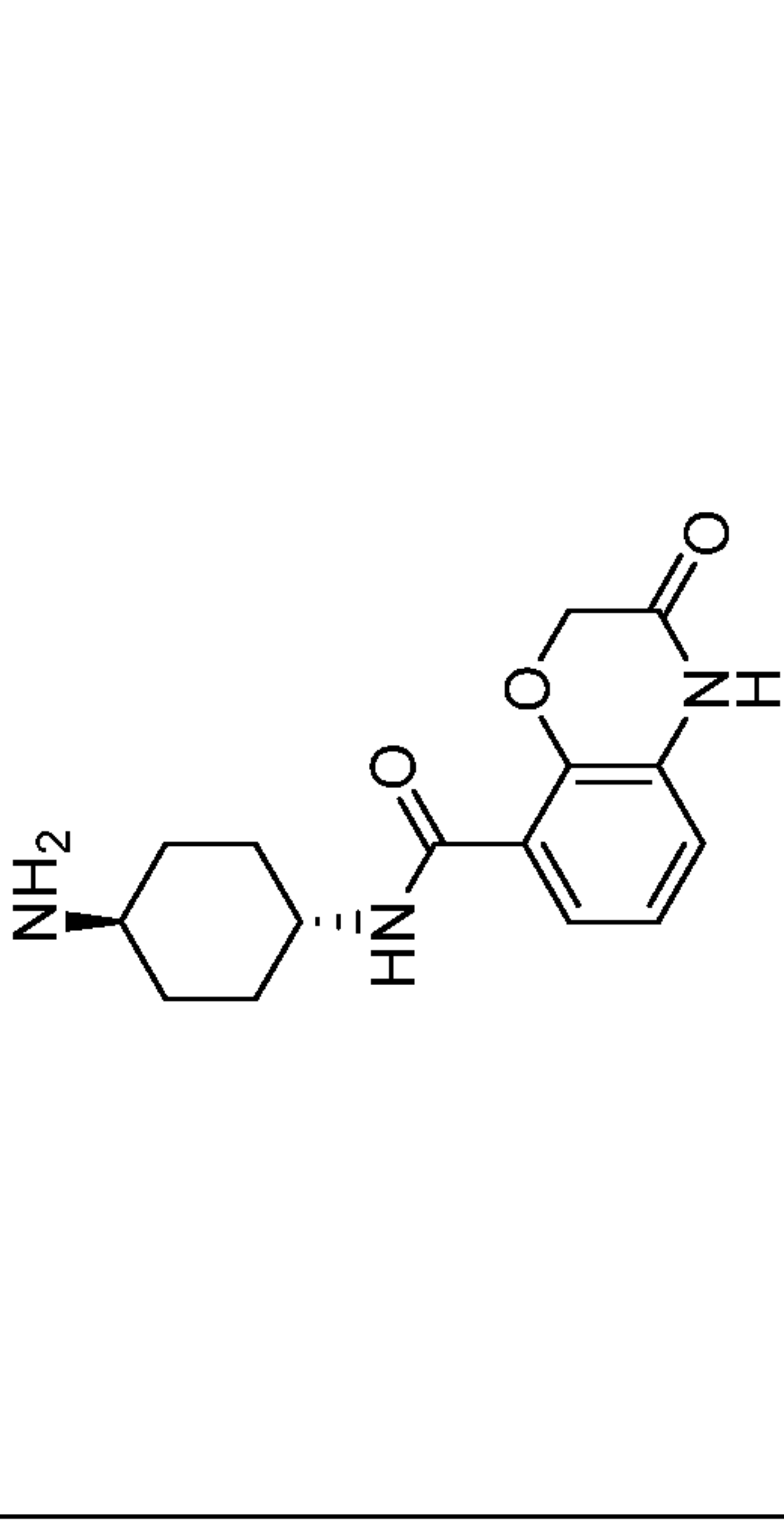
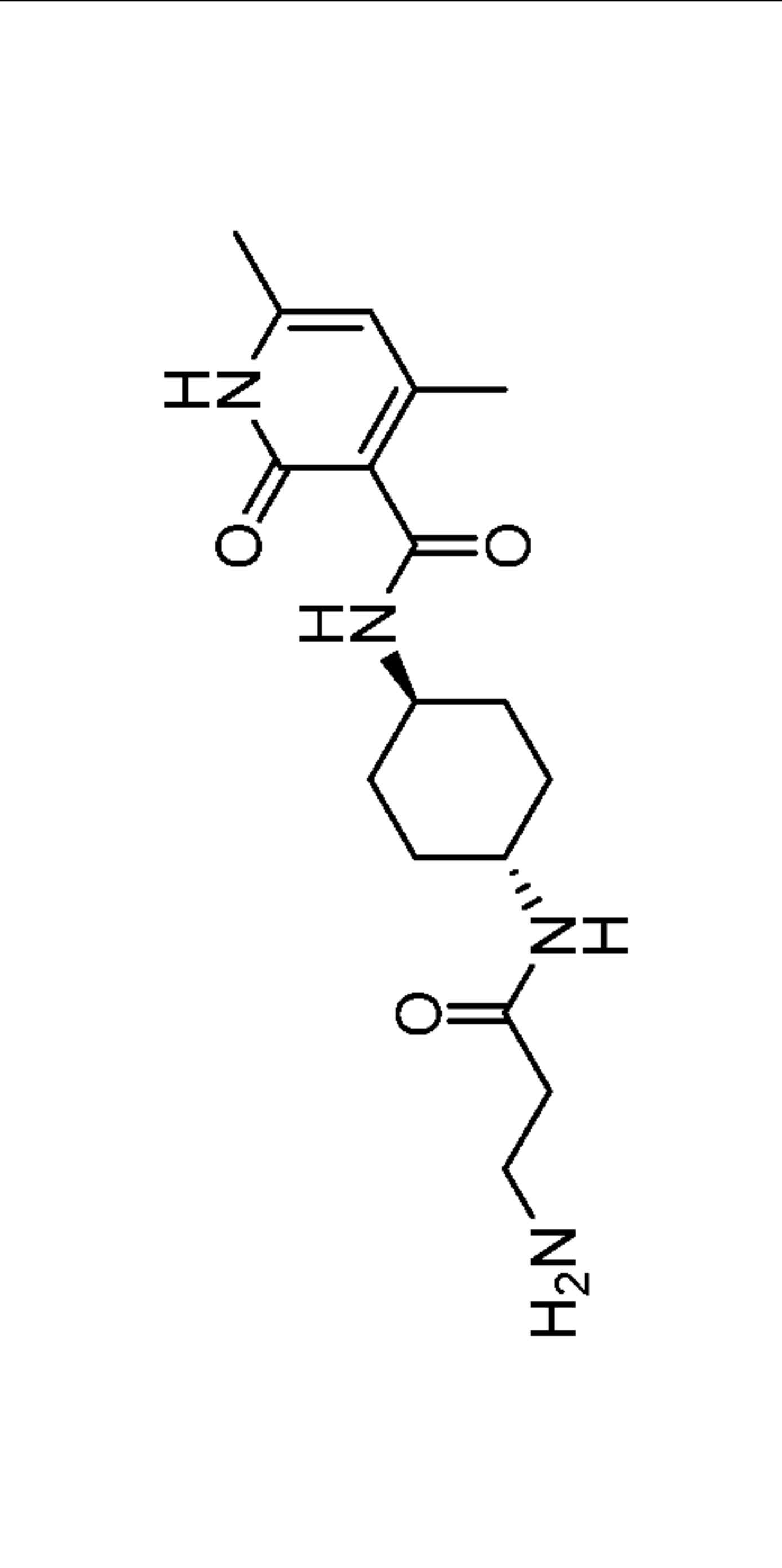
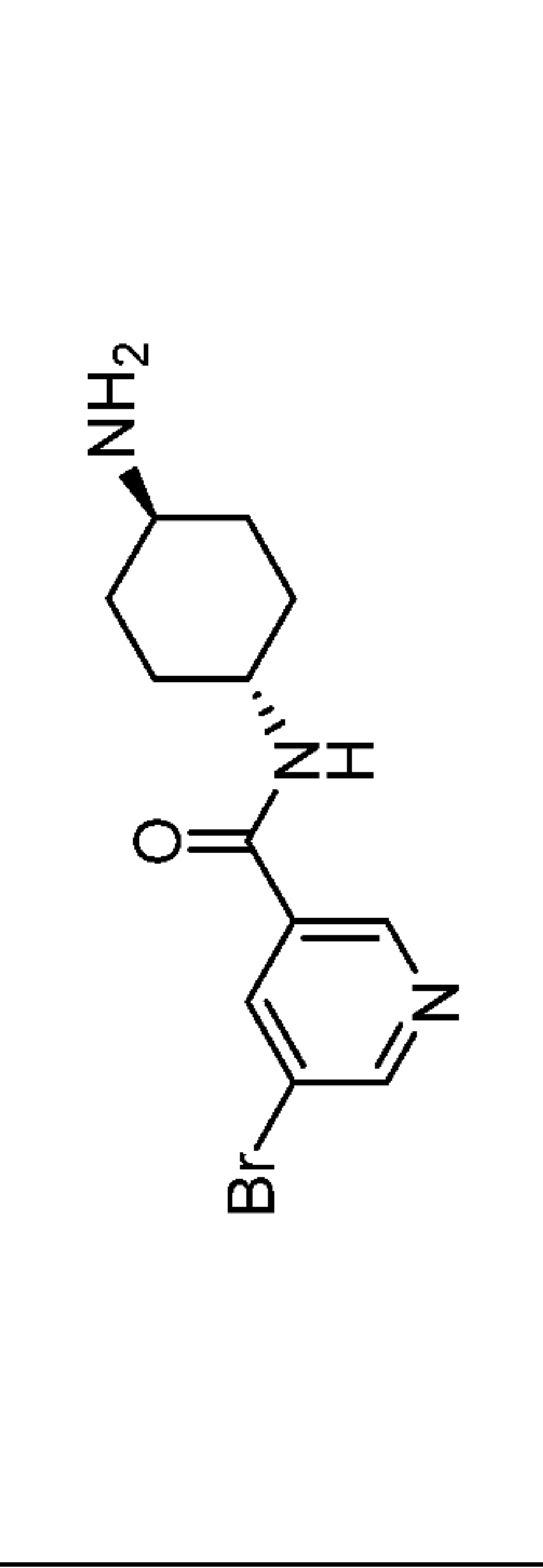
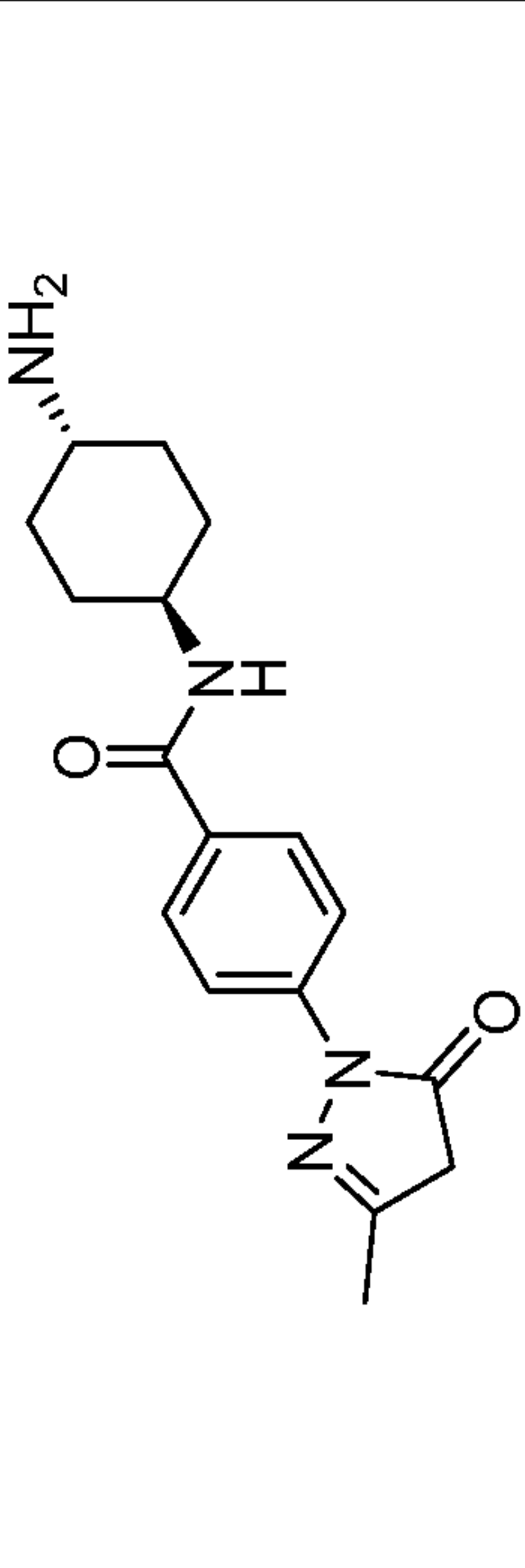
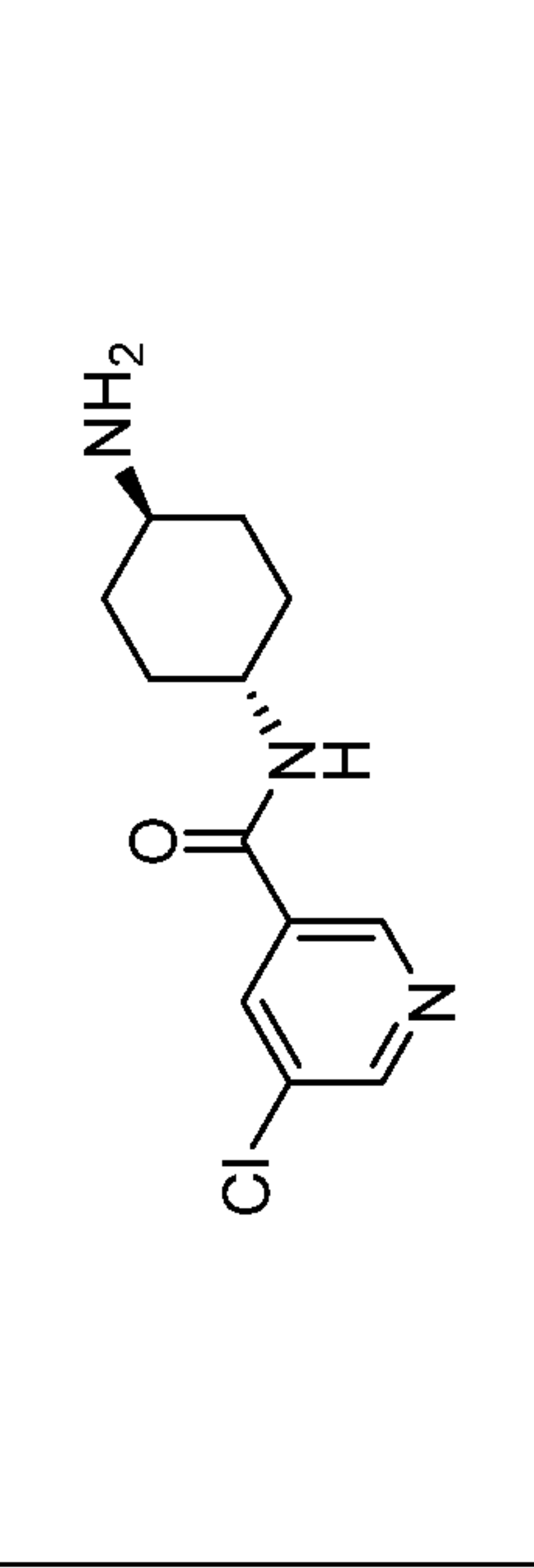
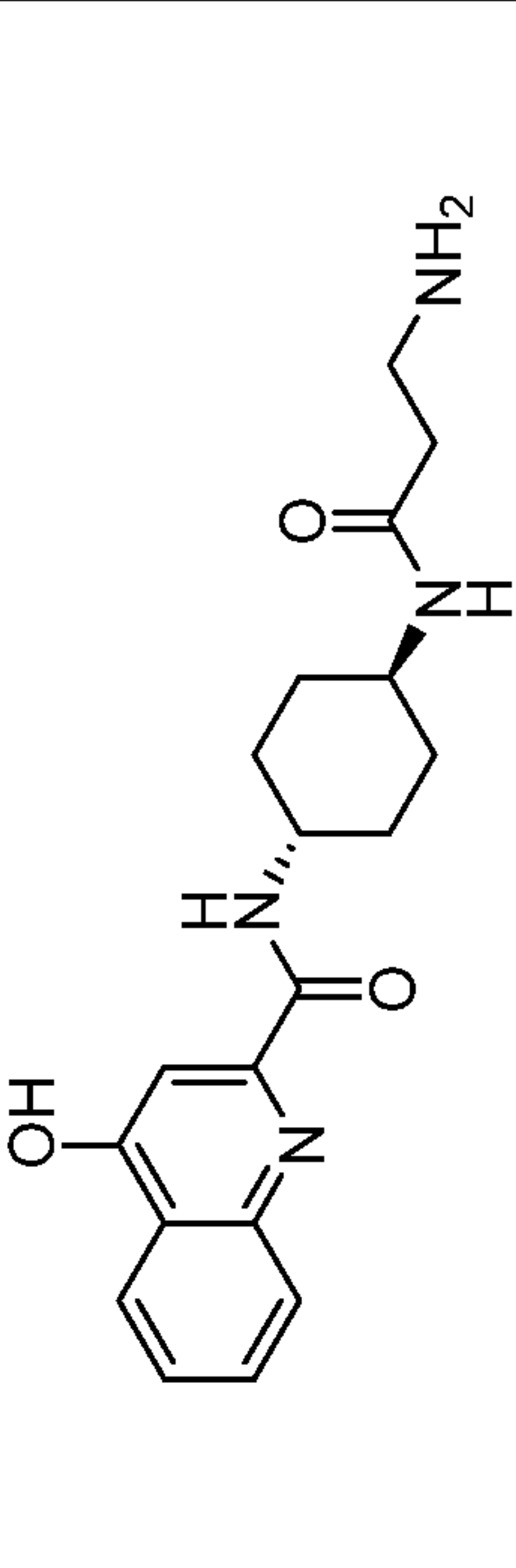
91		TFA	378		HCl
92		TFA	379		TFA
93		HCl	380		None
94		HCl	381		TFA
95		HCl	382		TFA

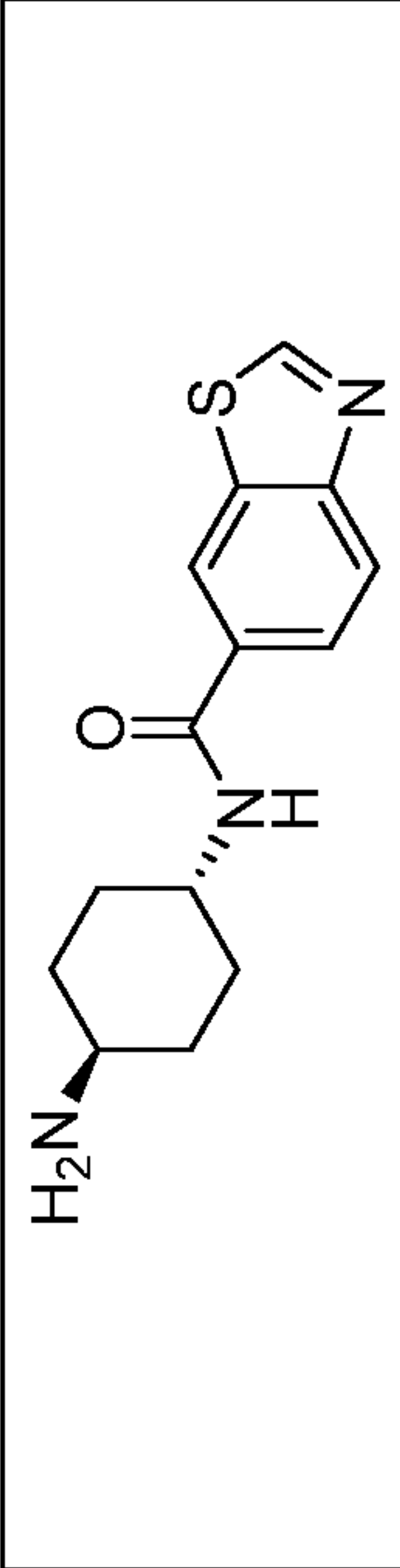
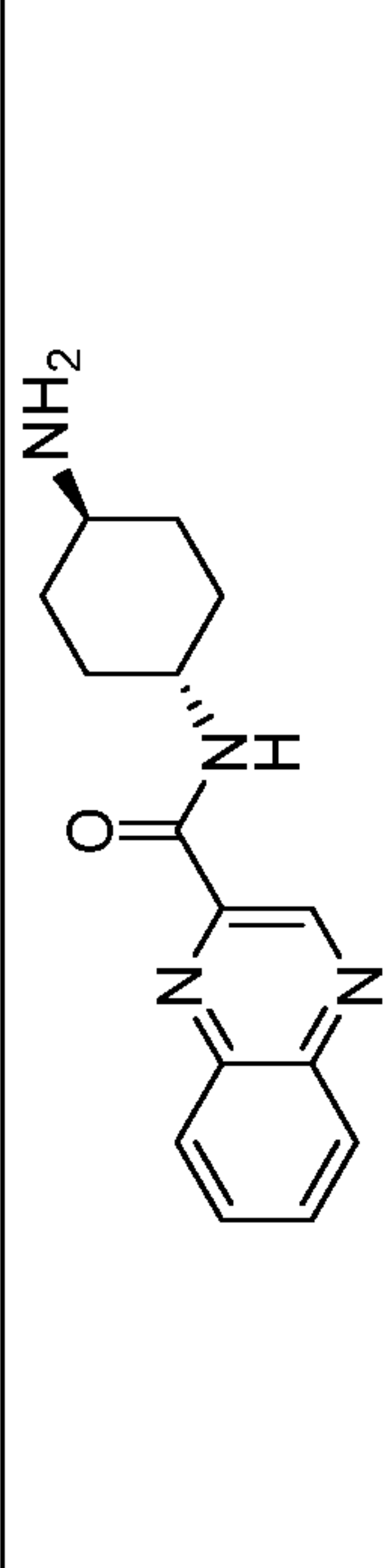
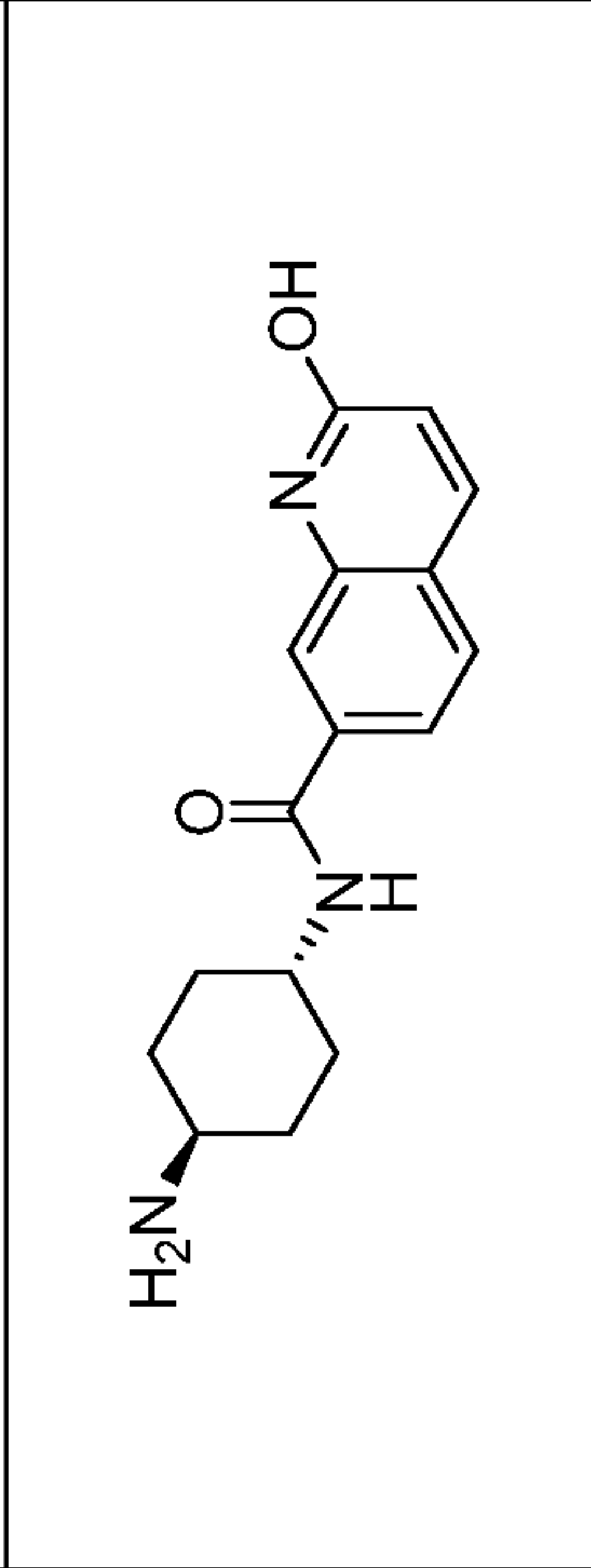
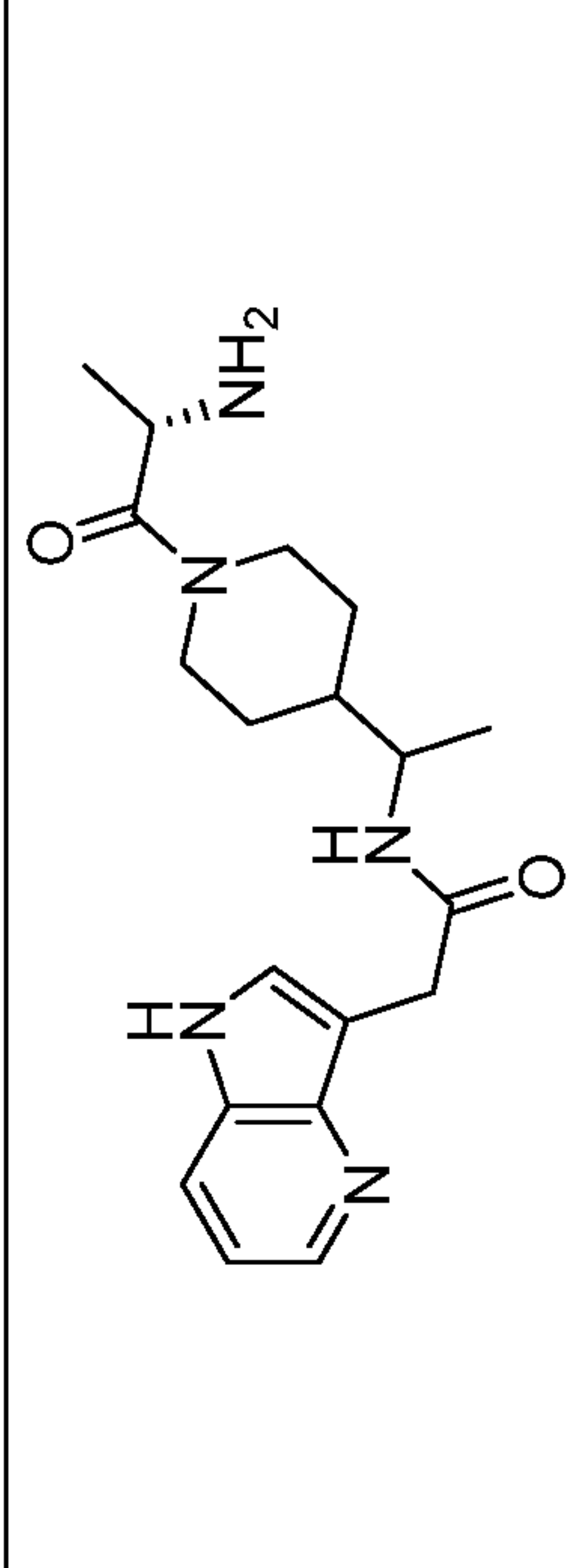
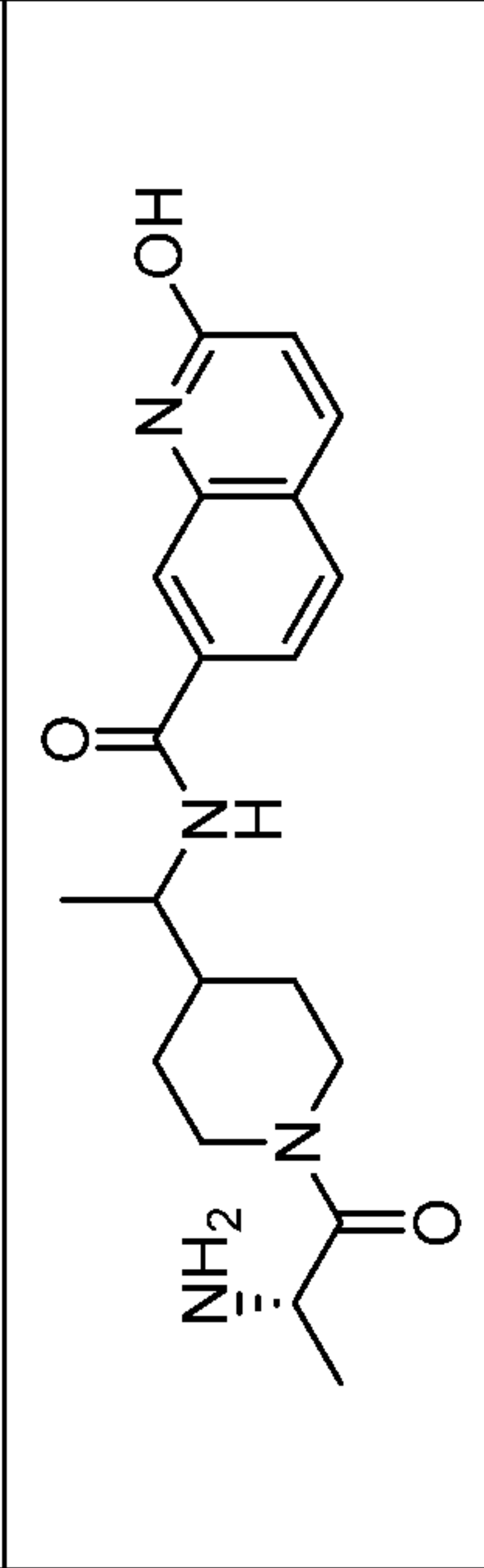
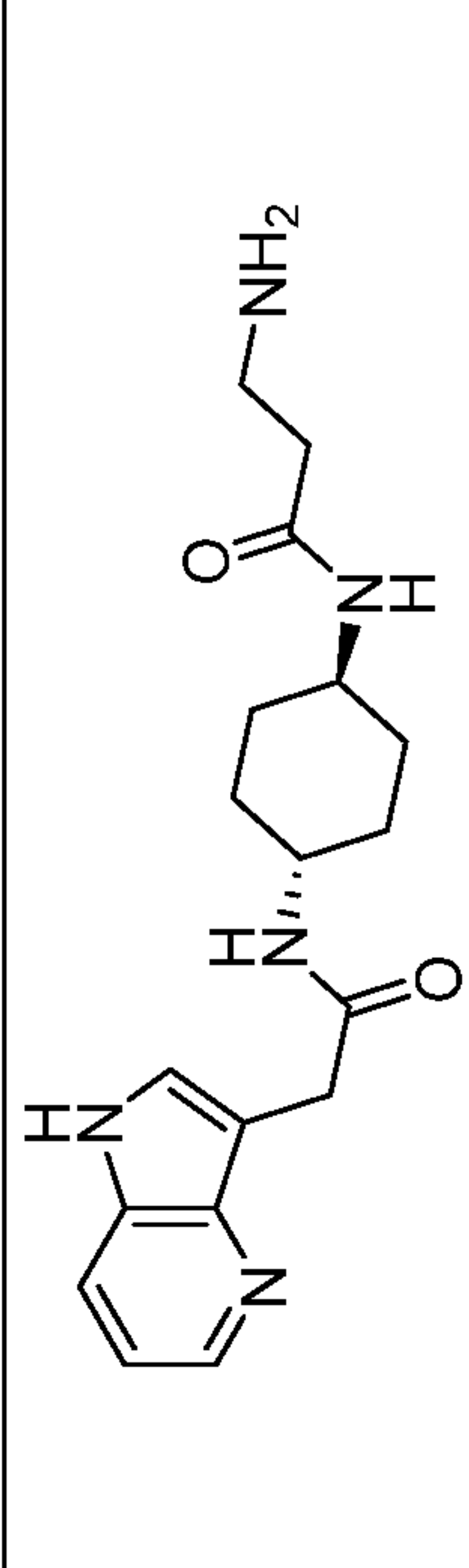
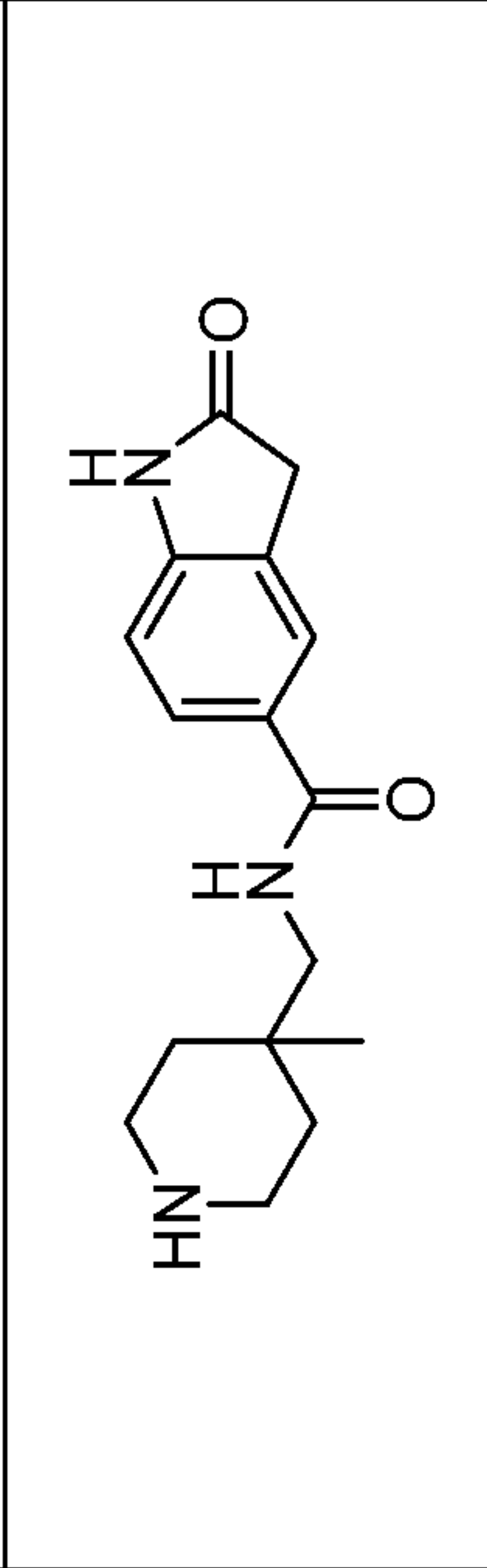
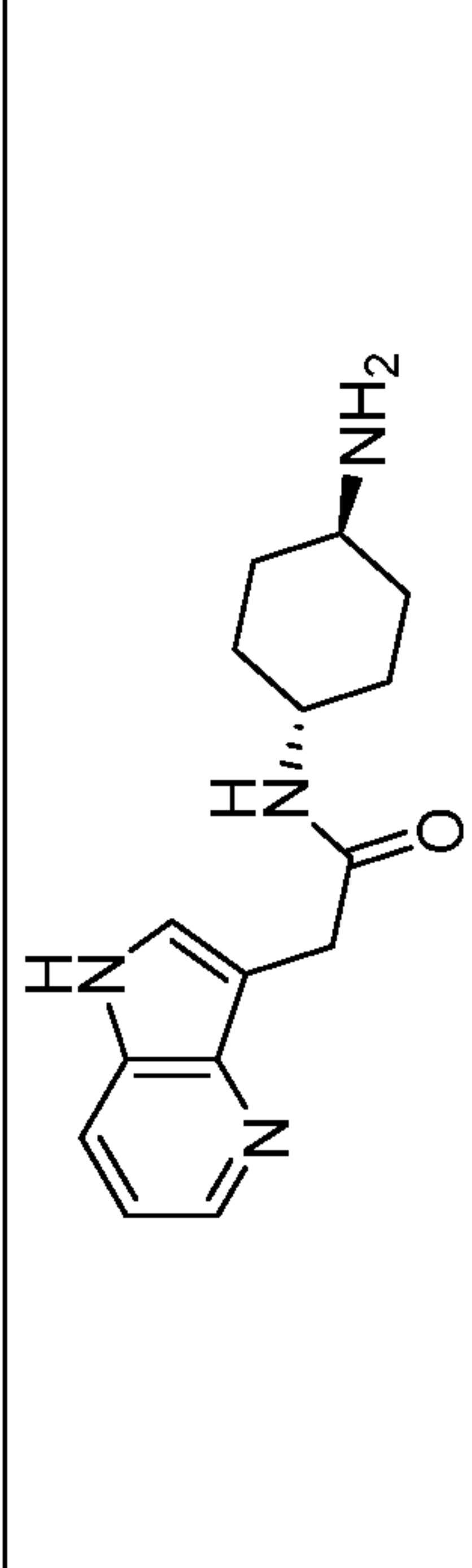
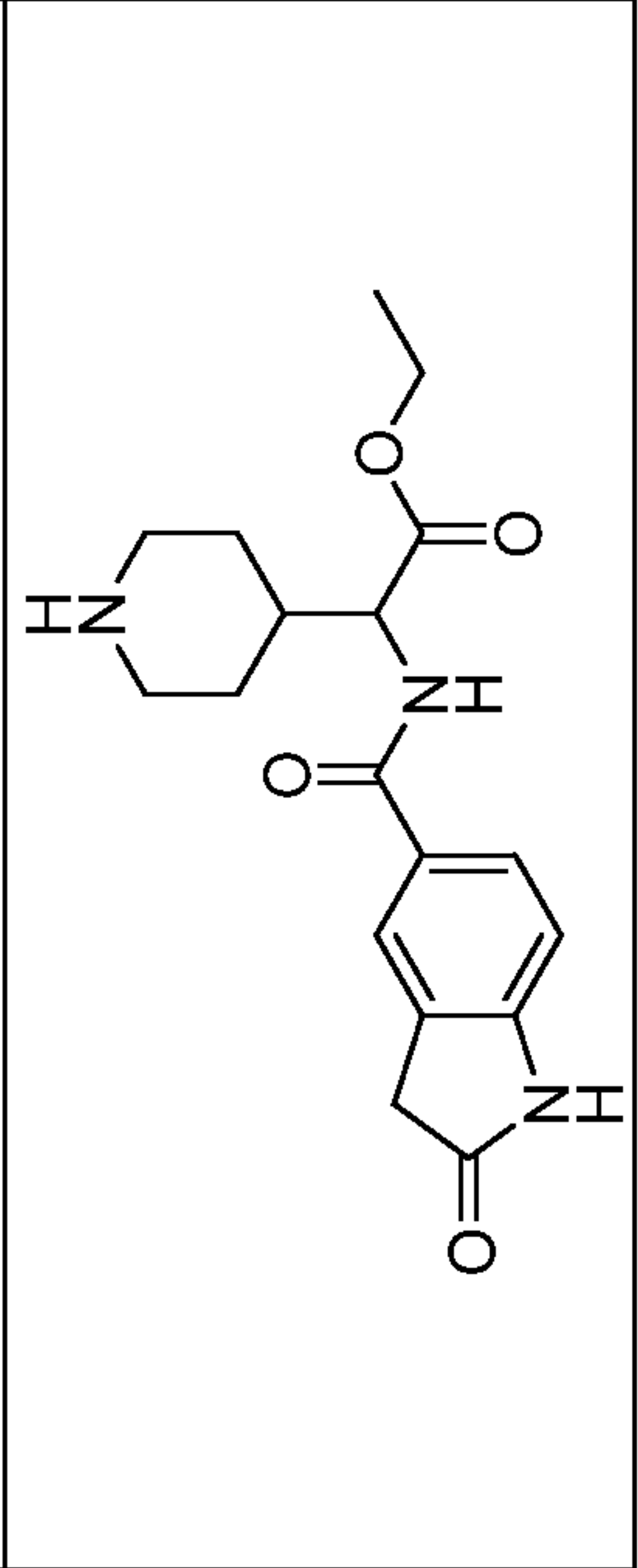
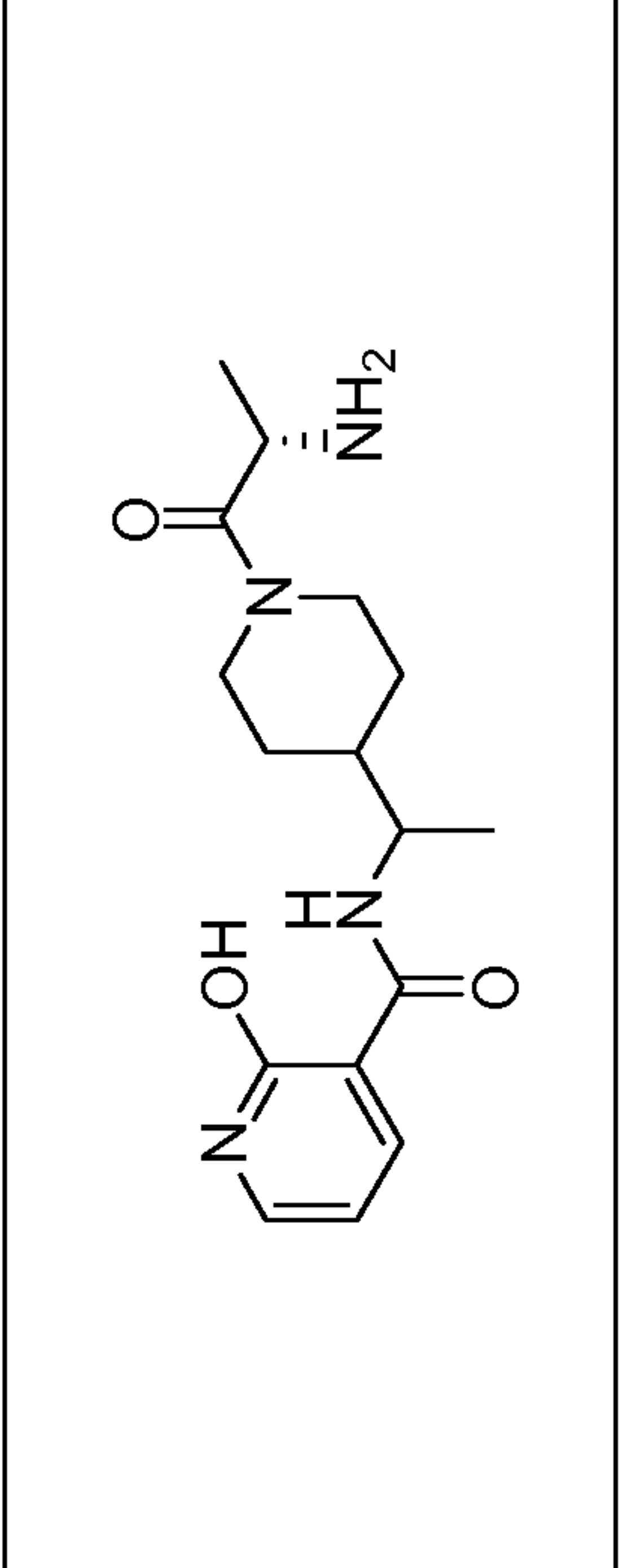
96		HCl	383		TFA
97		HCl	384		TFA
98		HCl	385		TFA
99		TFA	386		TFA
100		HCl	387		TFA

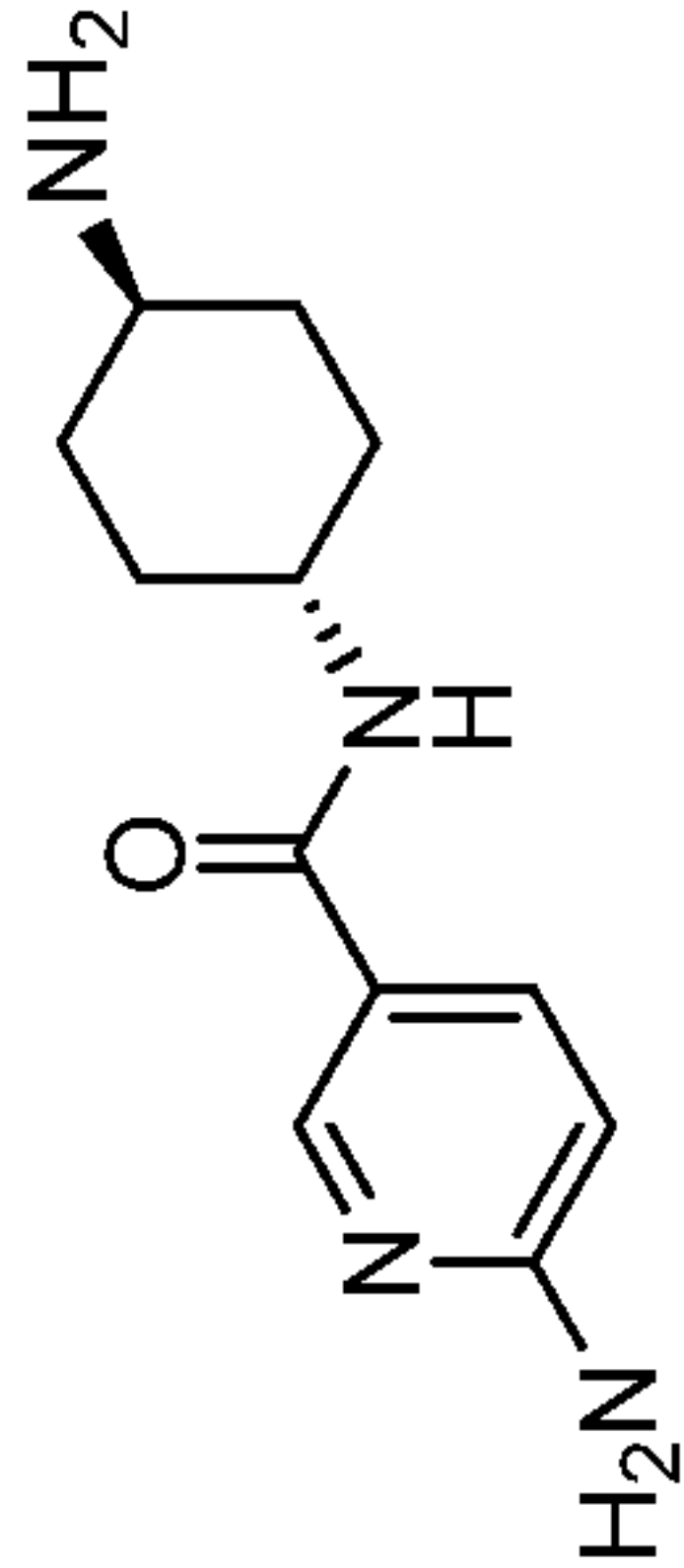
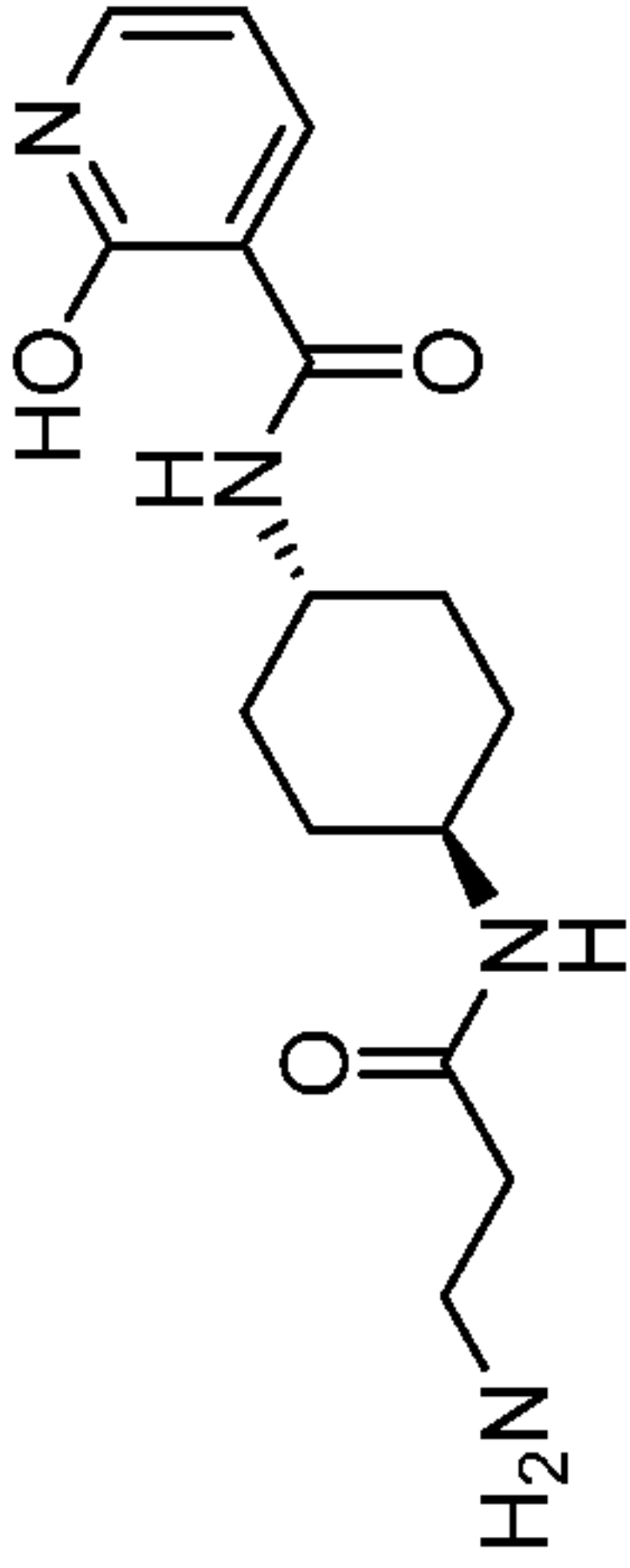
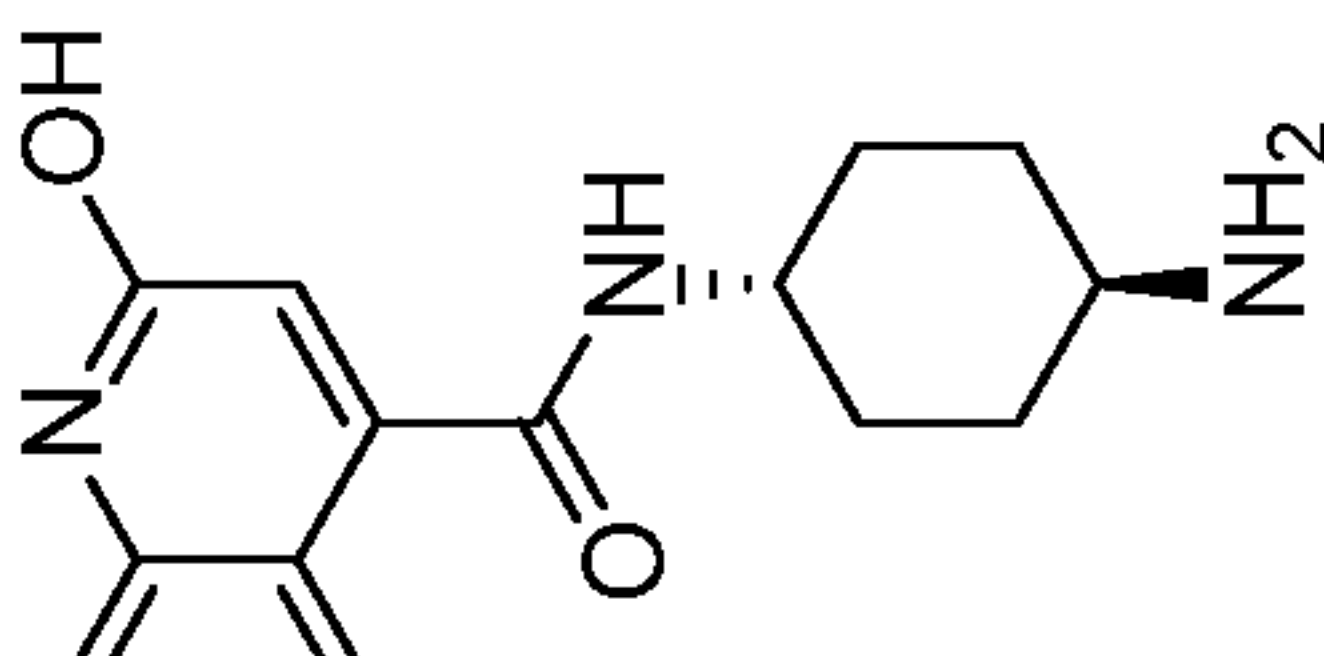
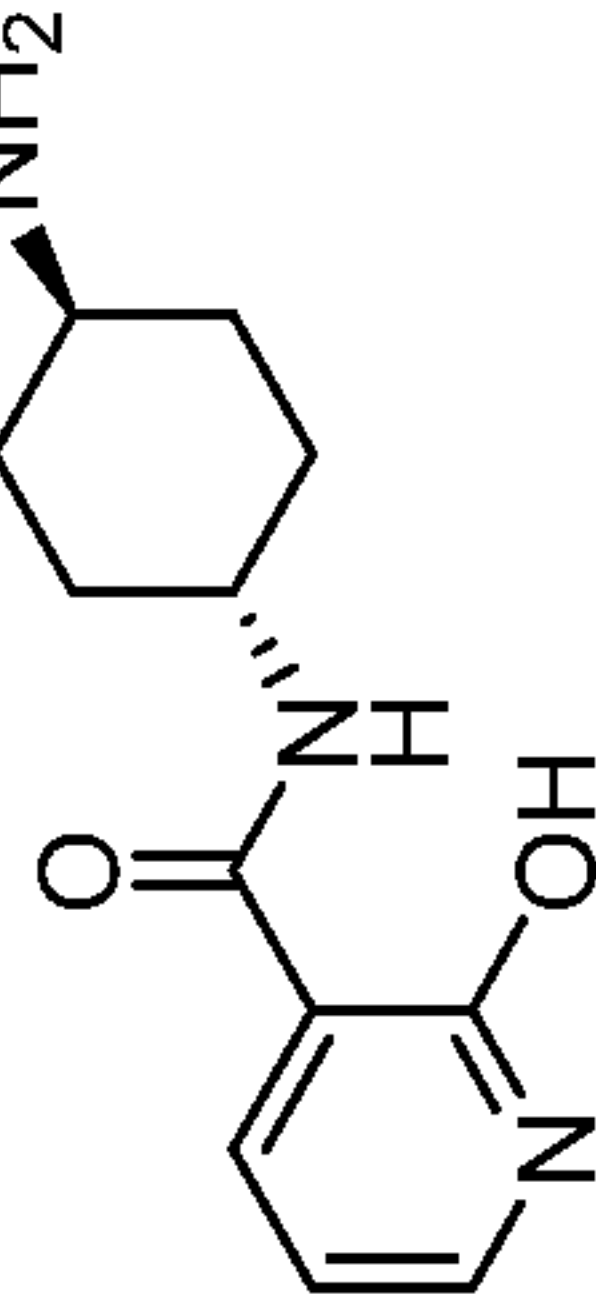
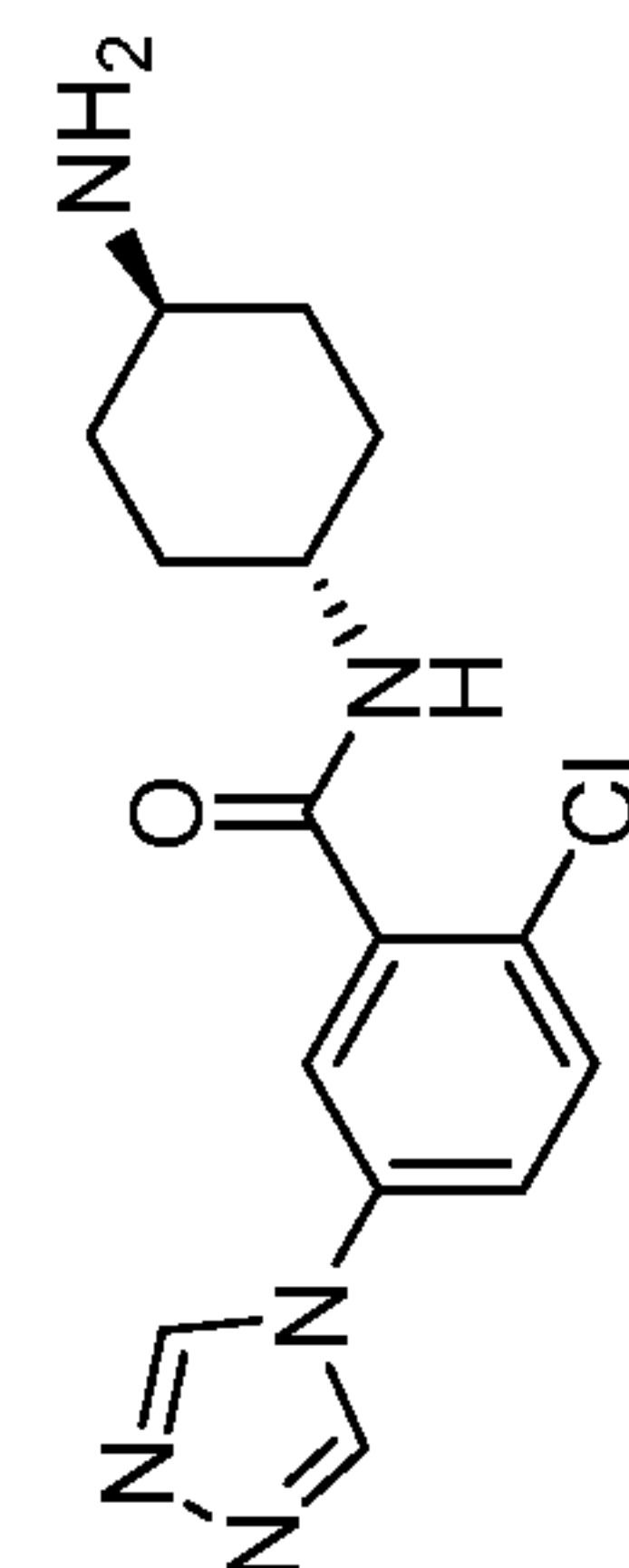
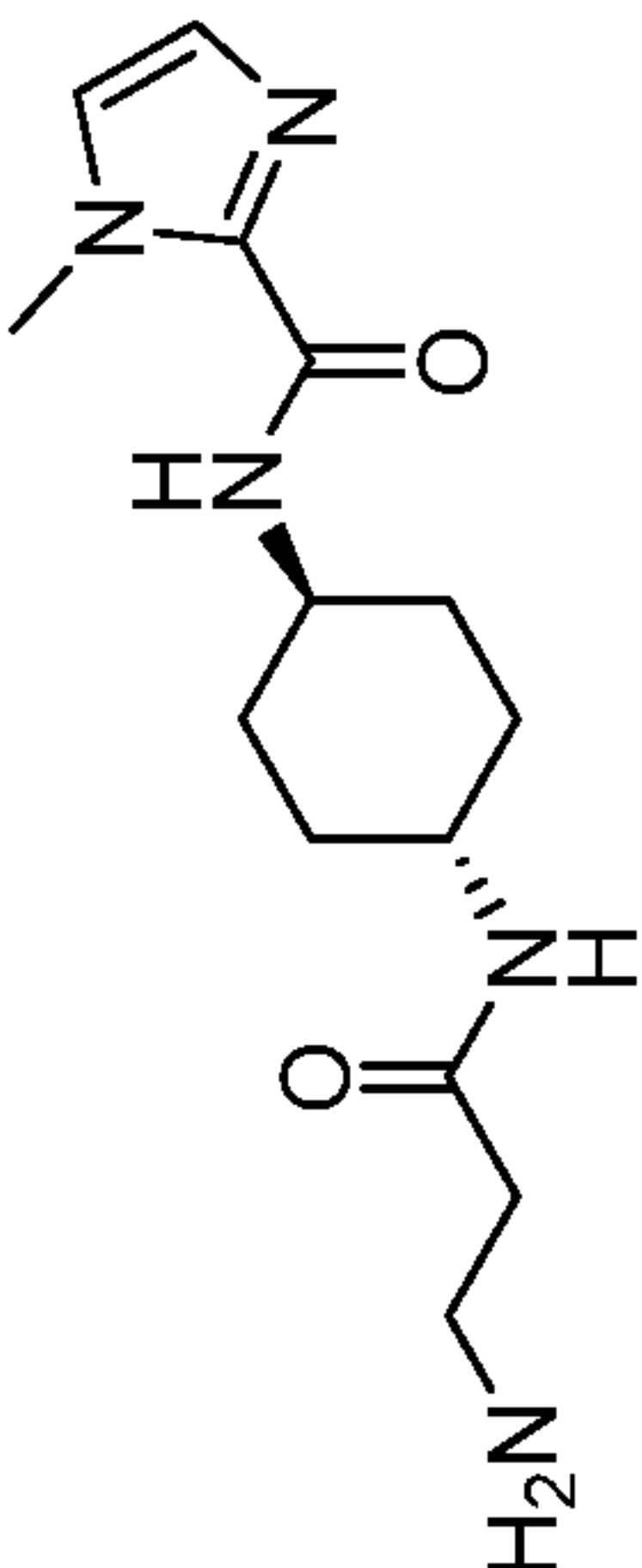
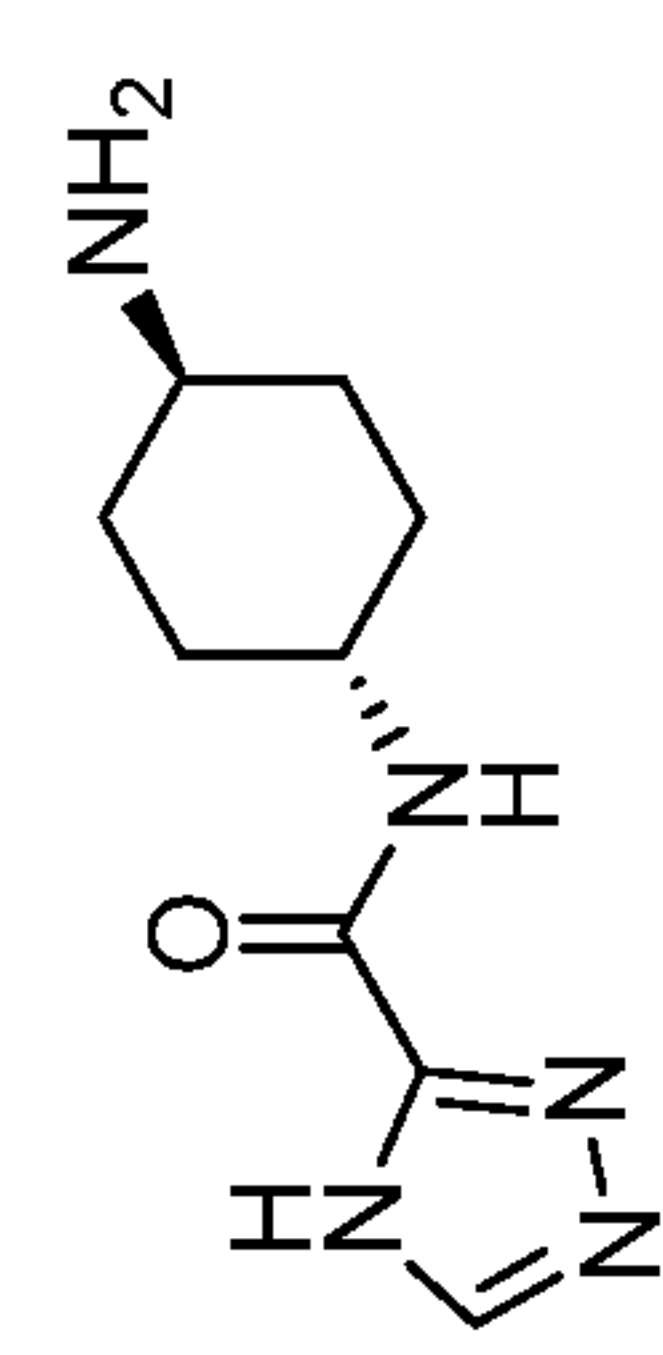
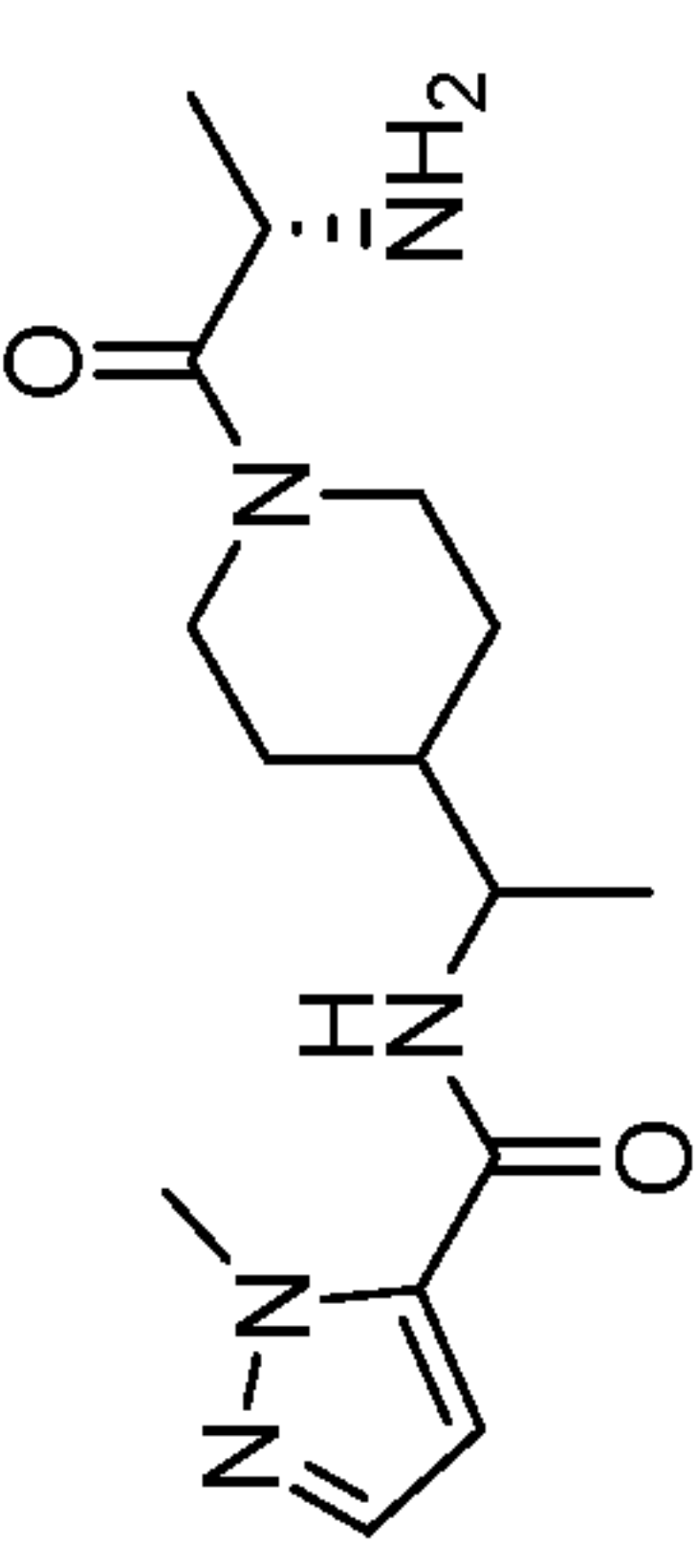
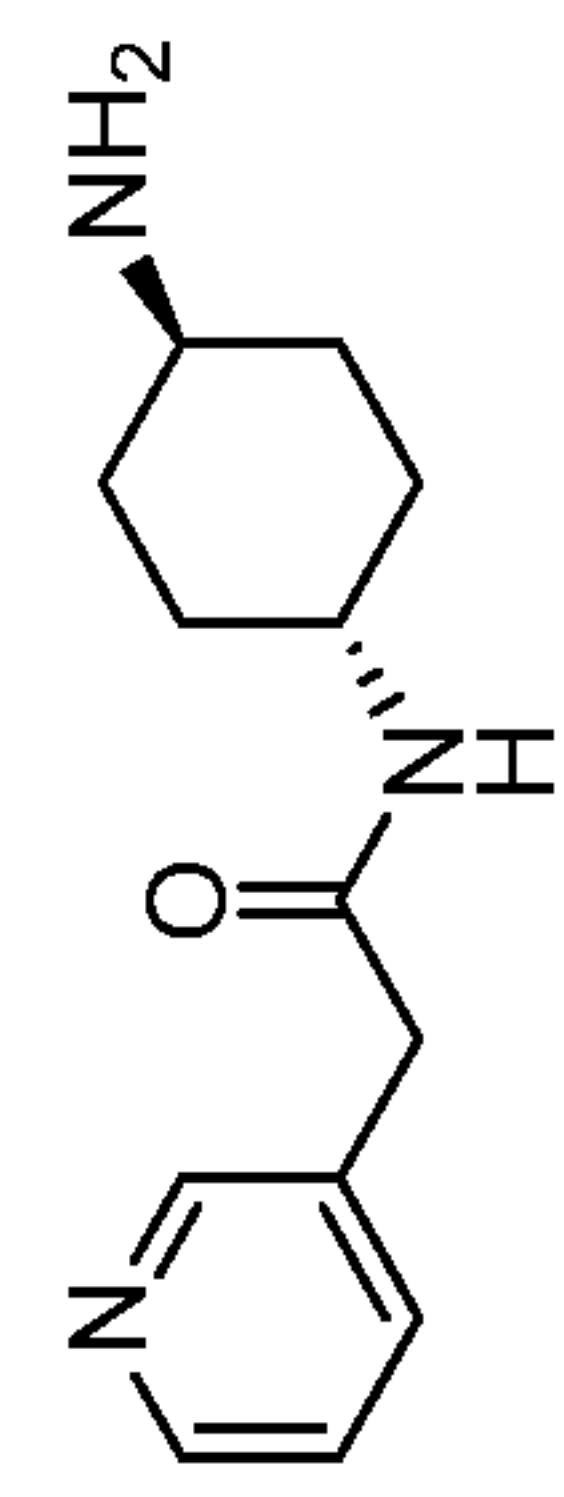
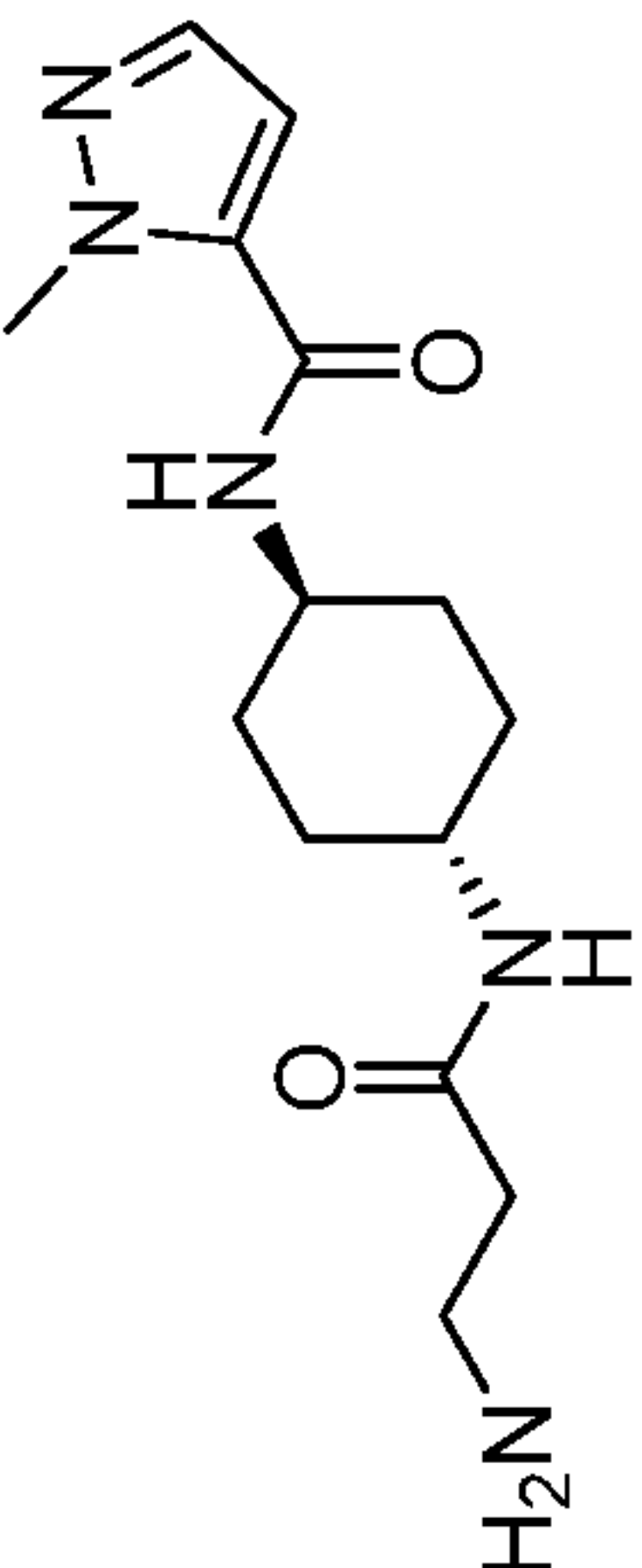
101		HCl	388		None
102		HCl	389		TFA
103		TFA	390		HCl
104		TFA	391		TFA

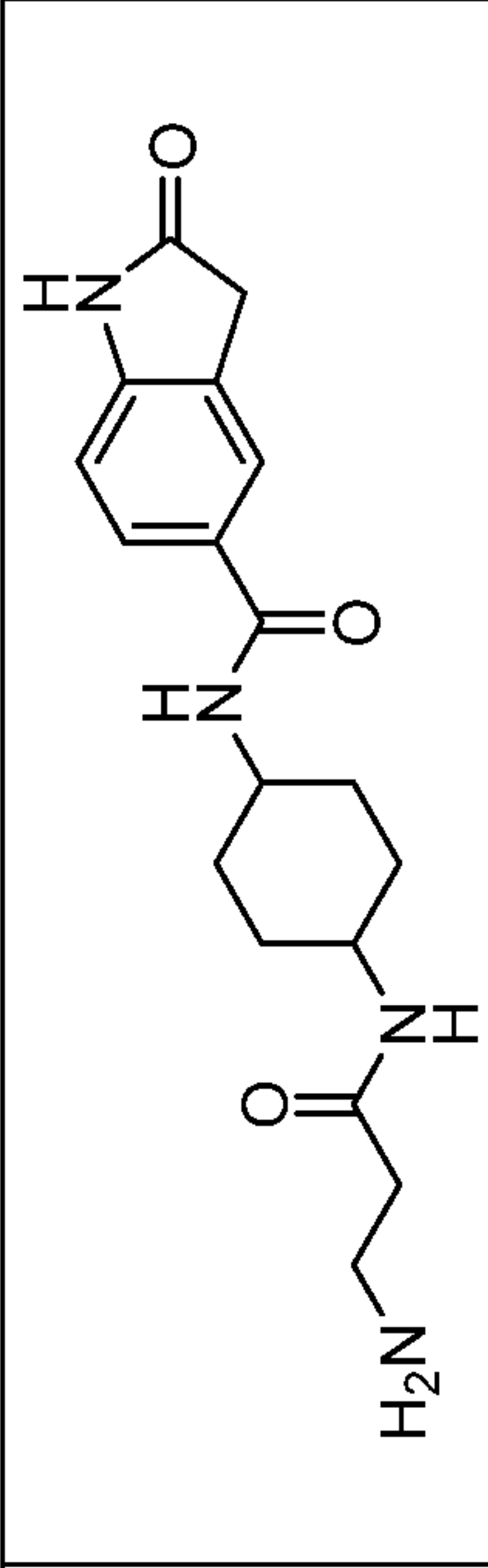
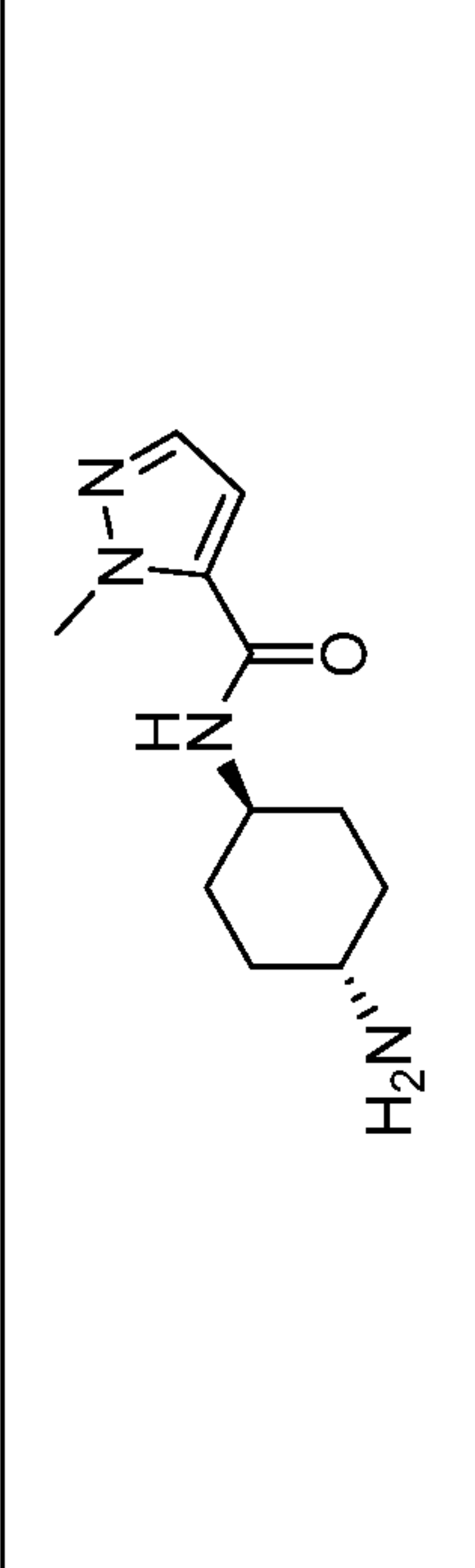
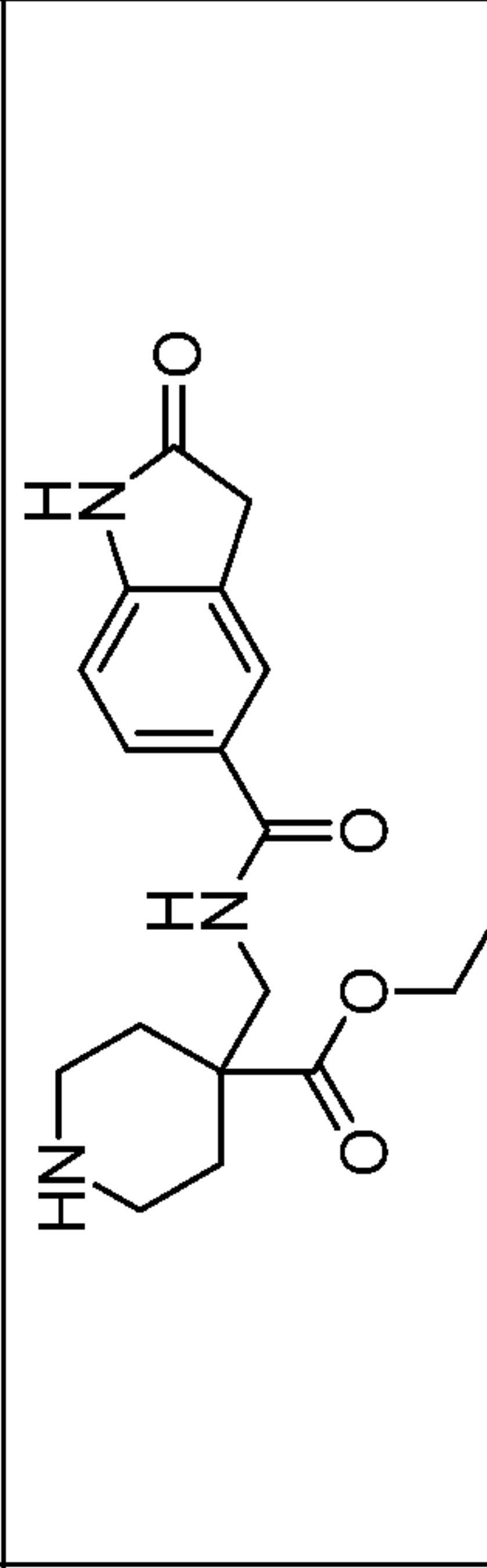
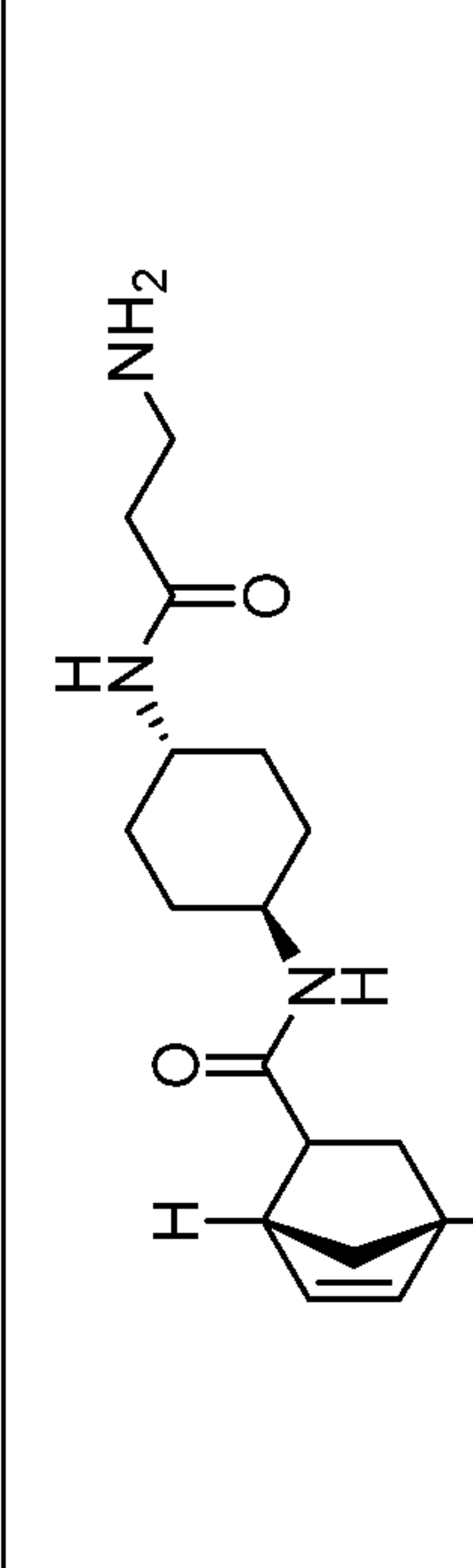
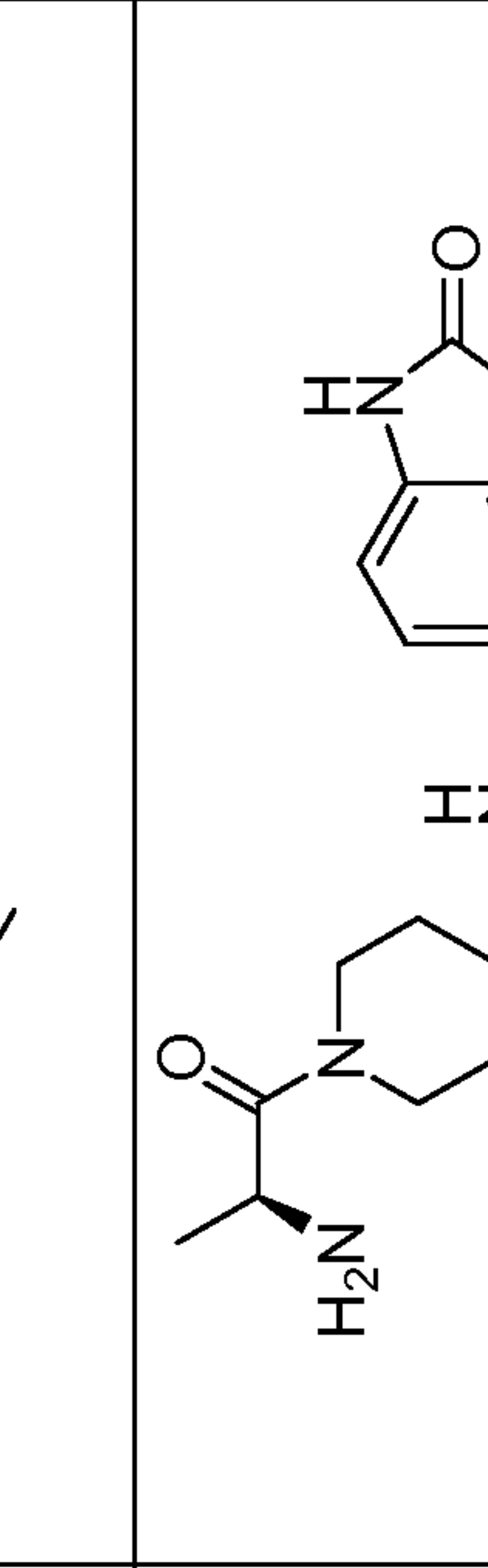
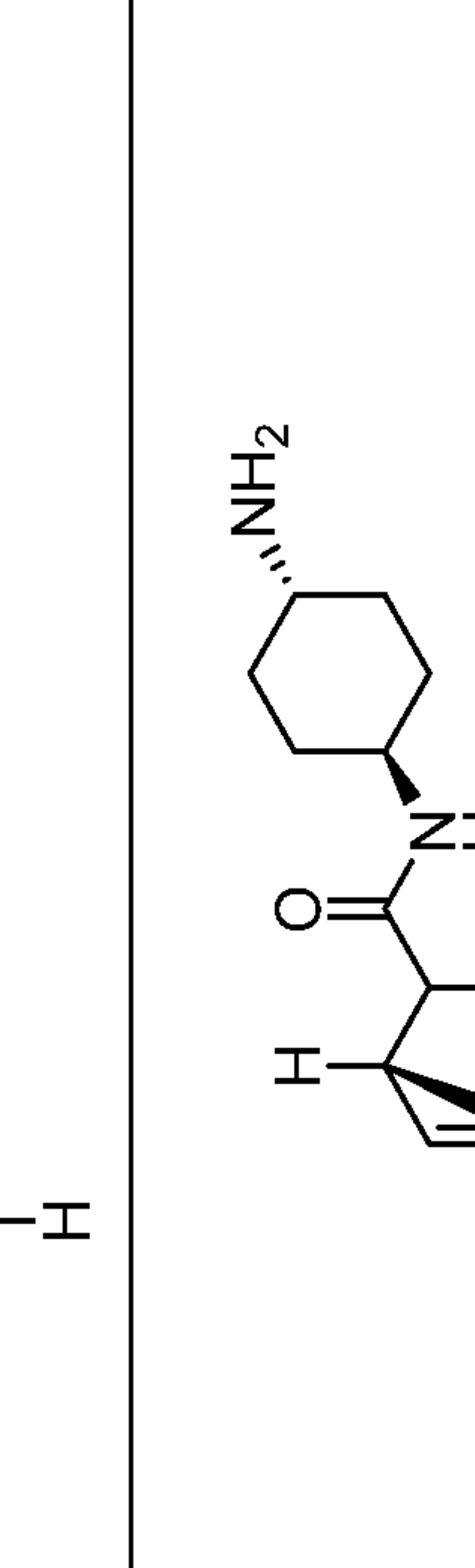
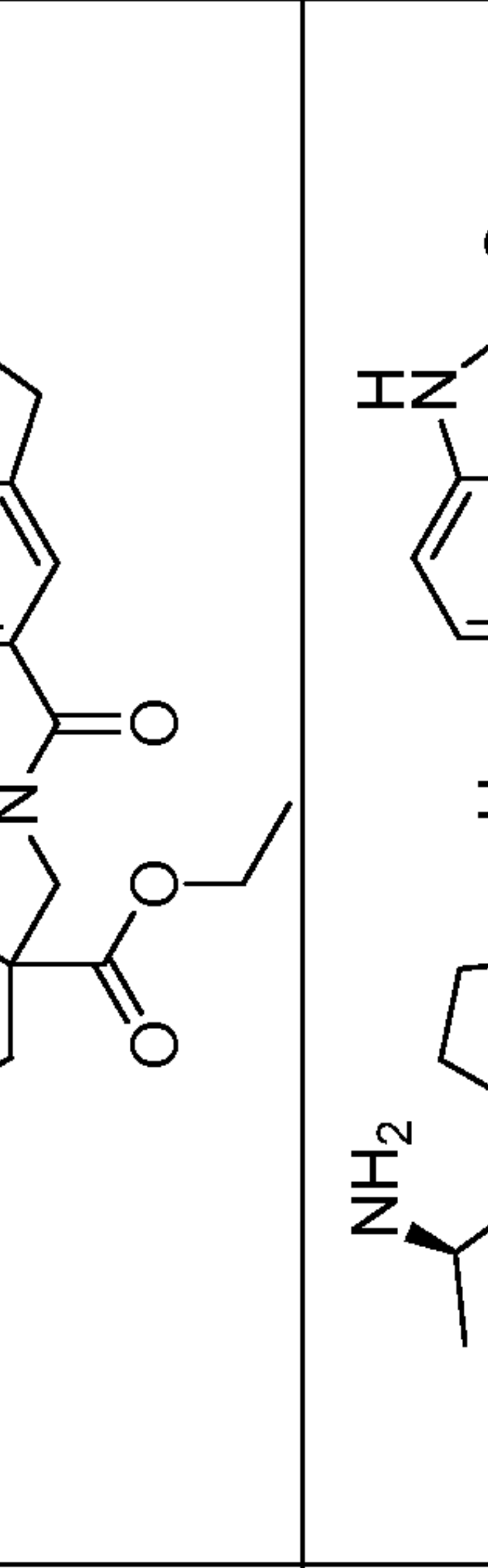
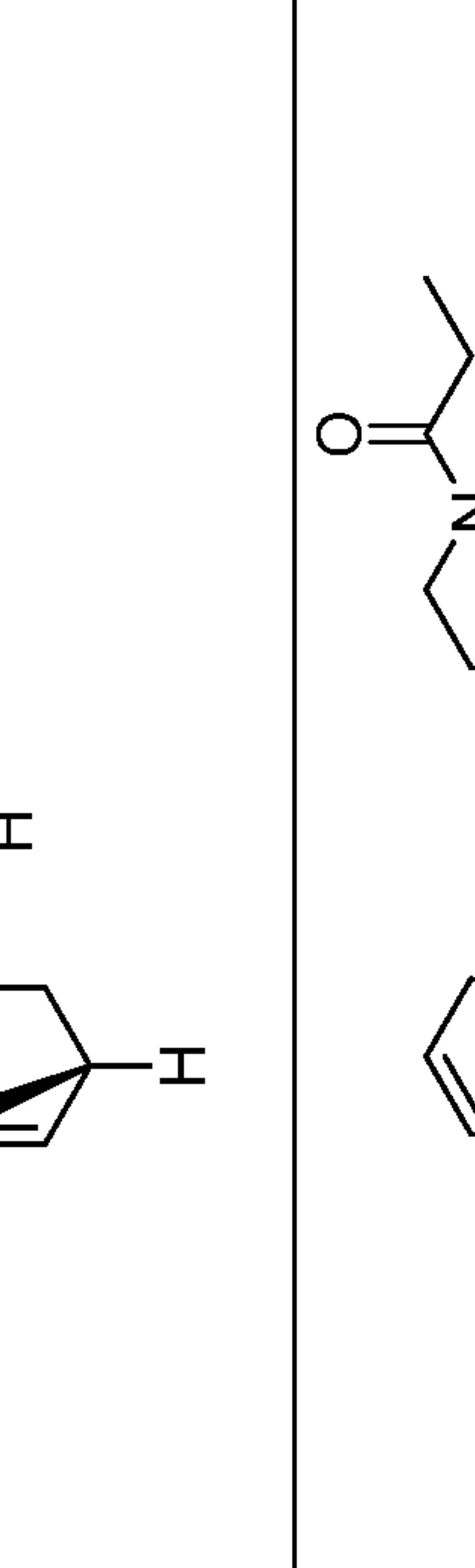
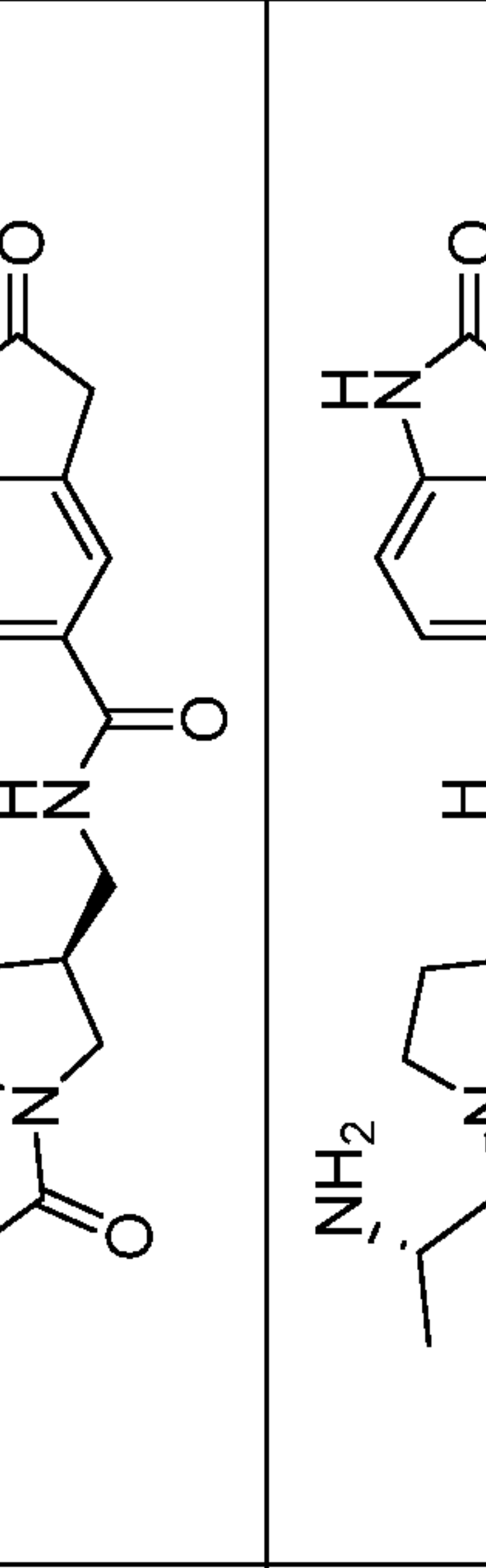
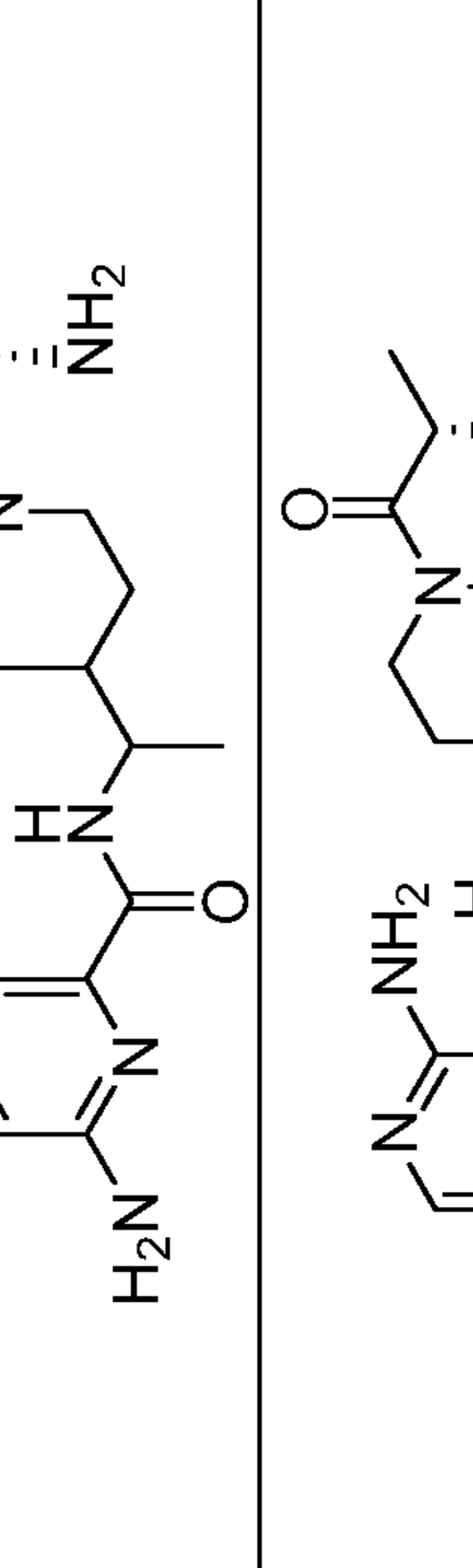
105		TFA	392		TFA
106		TFA	393		TFA
107		TFA	394		None
108		HCl	395		HCl
109		HCl	396		TFA

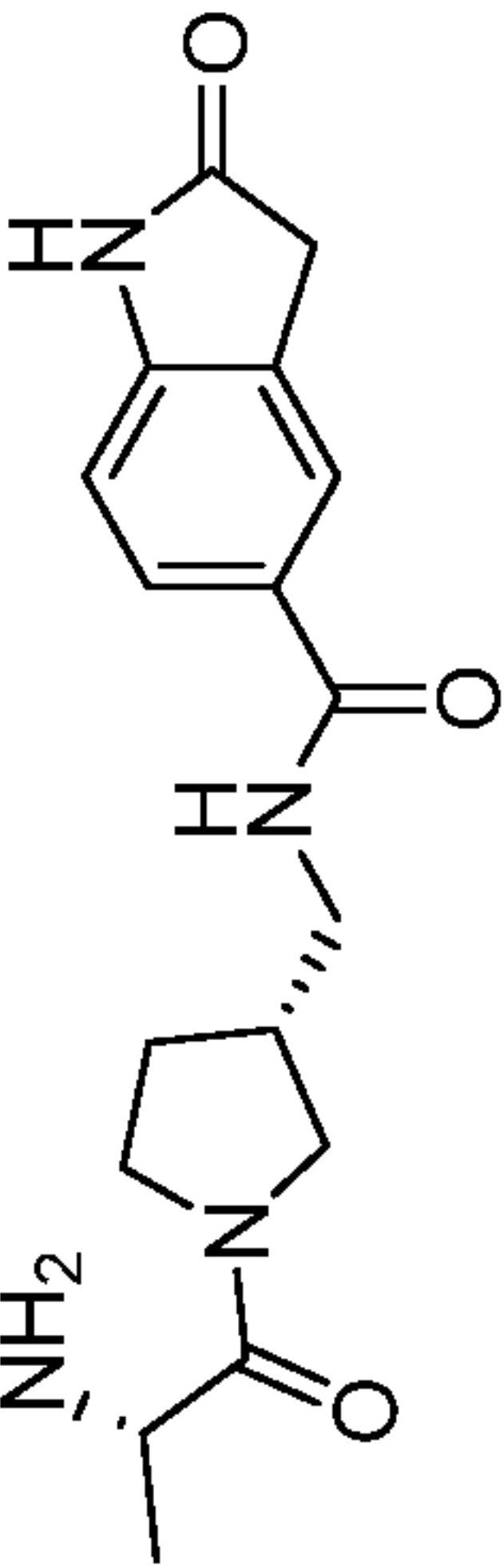
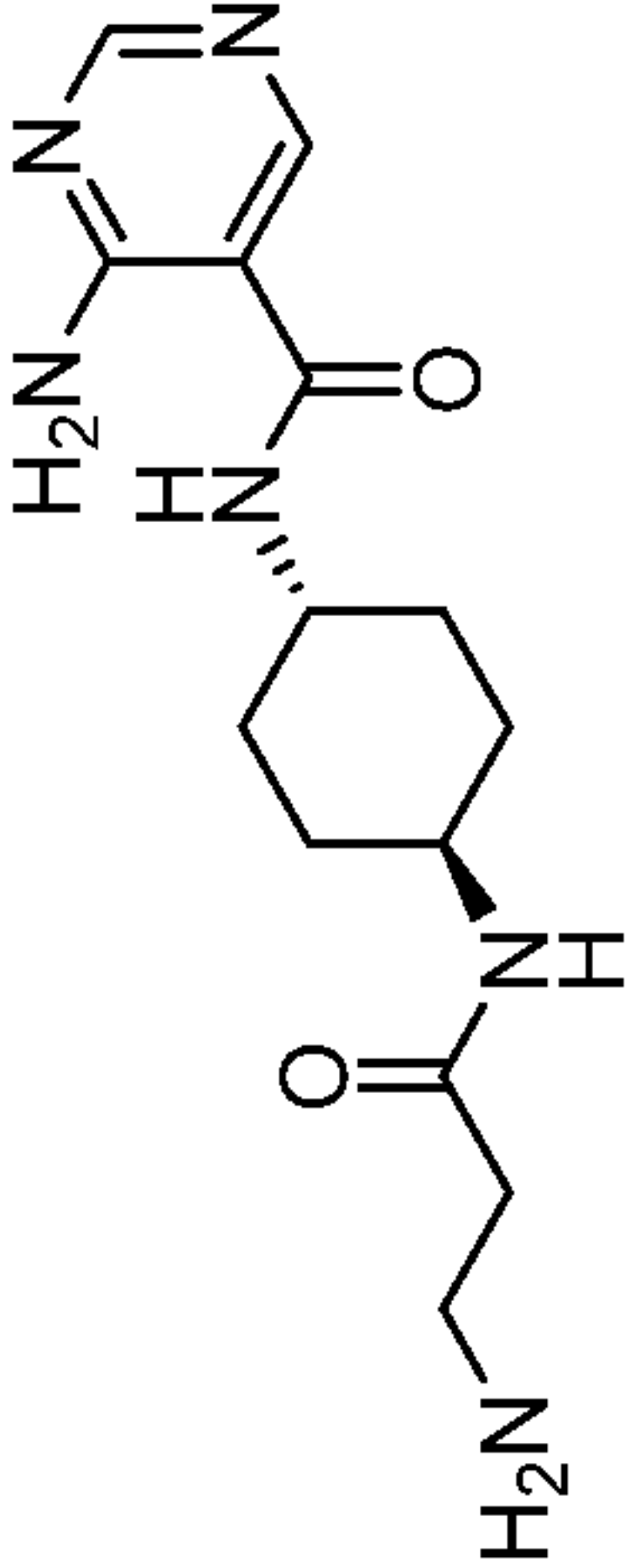
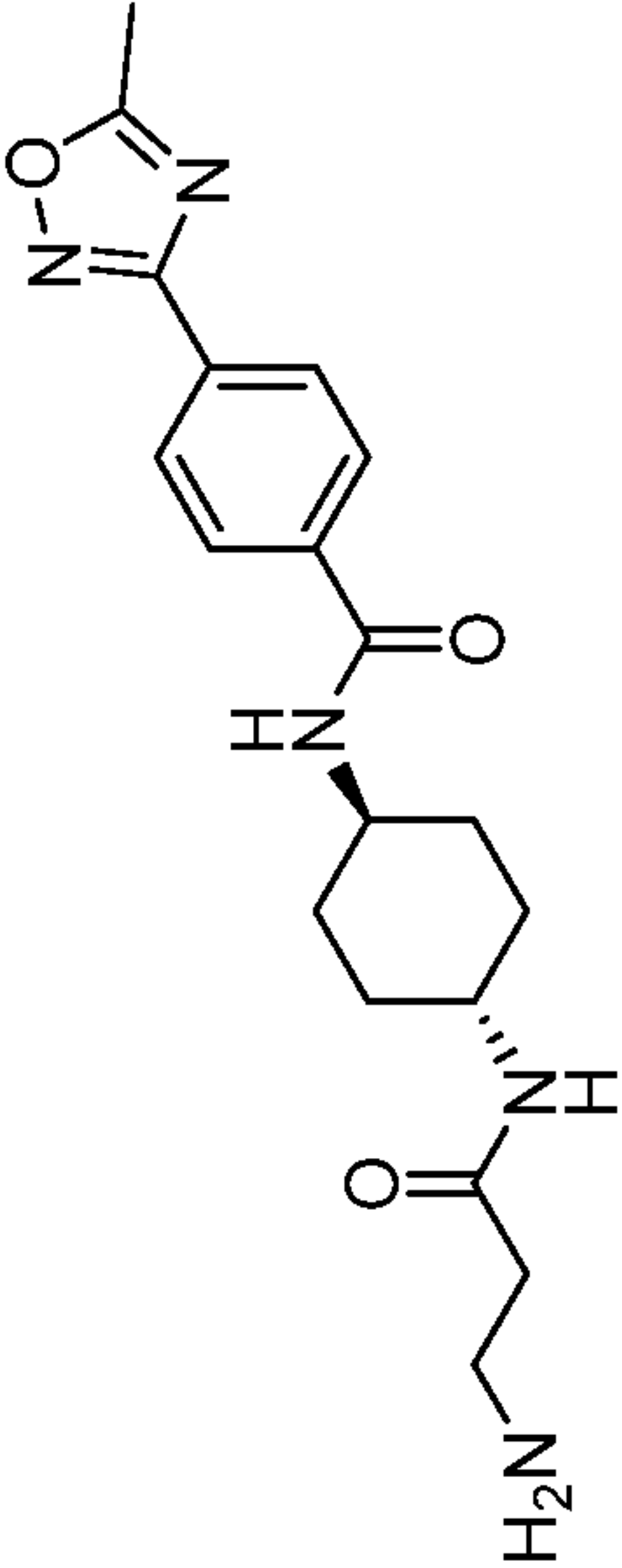
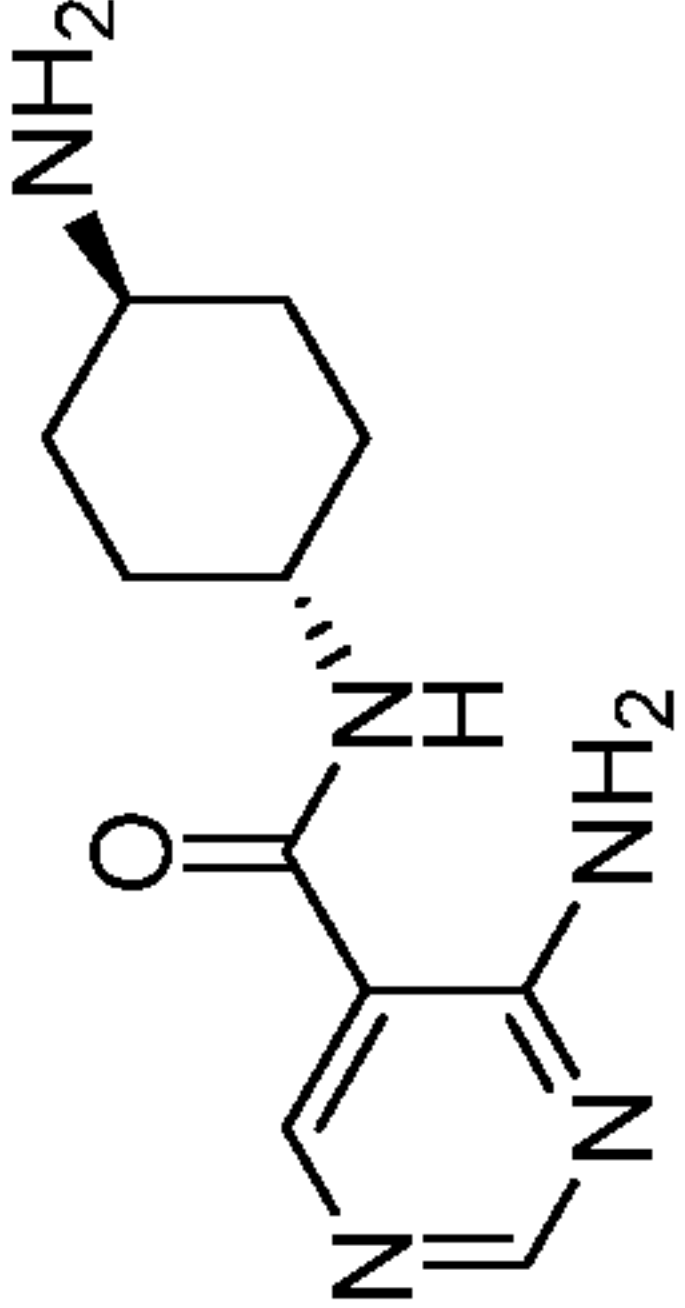
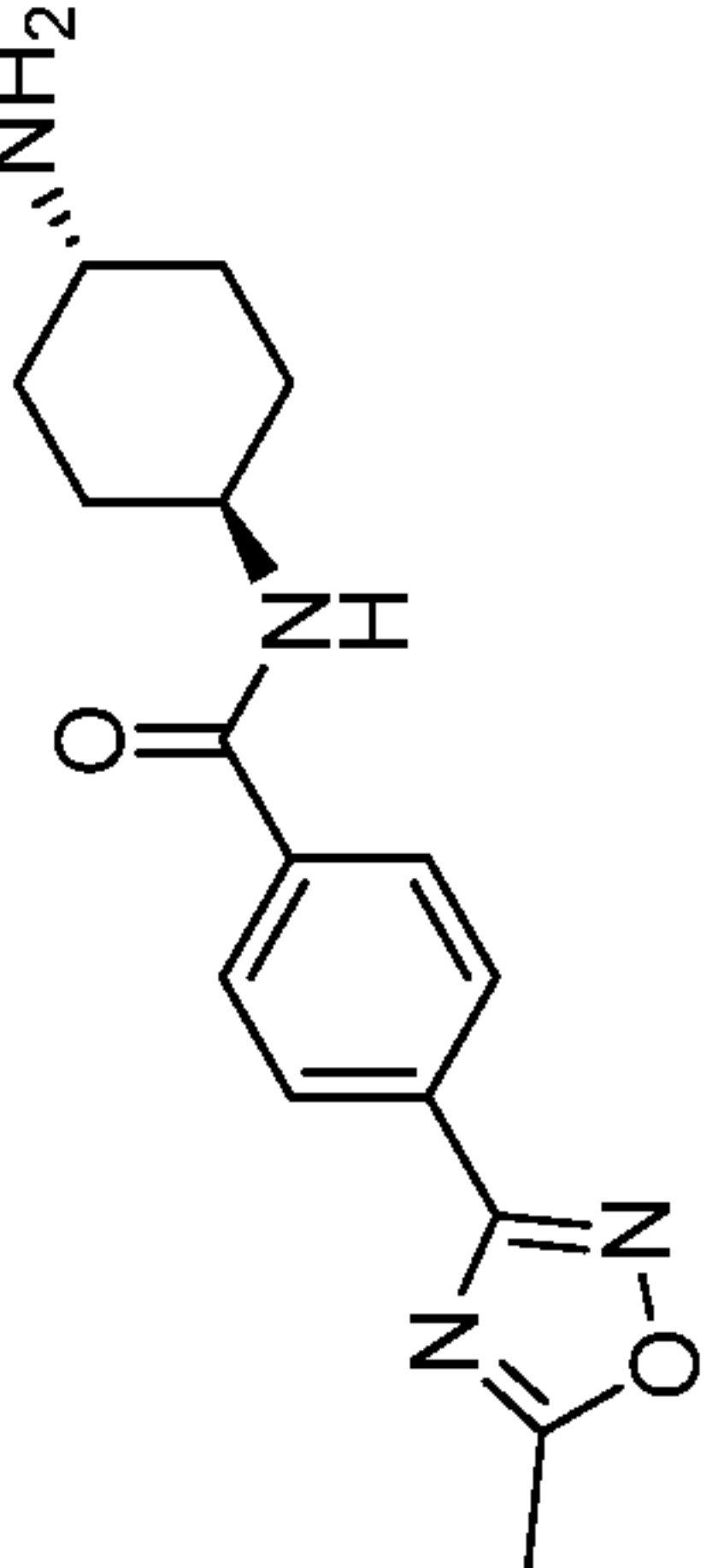
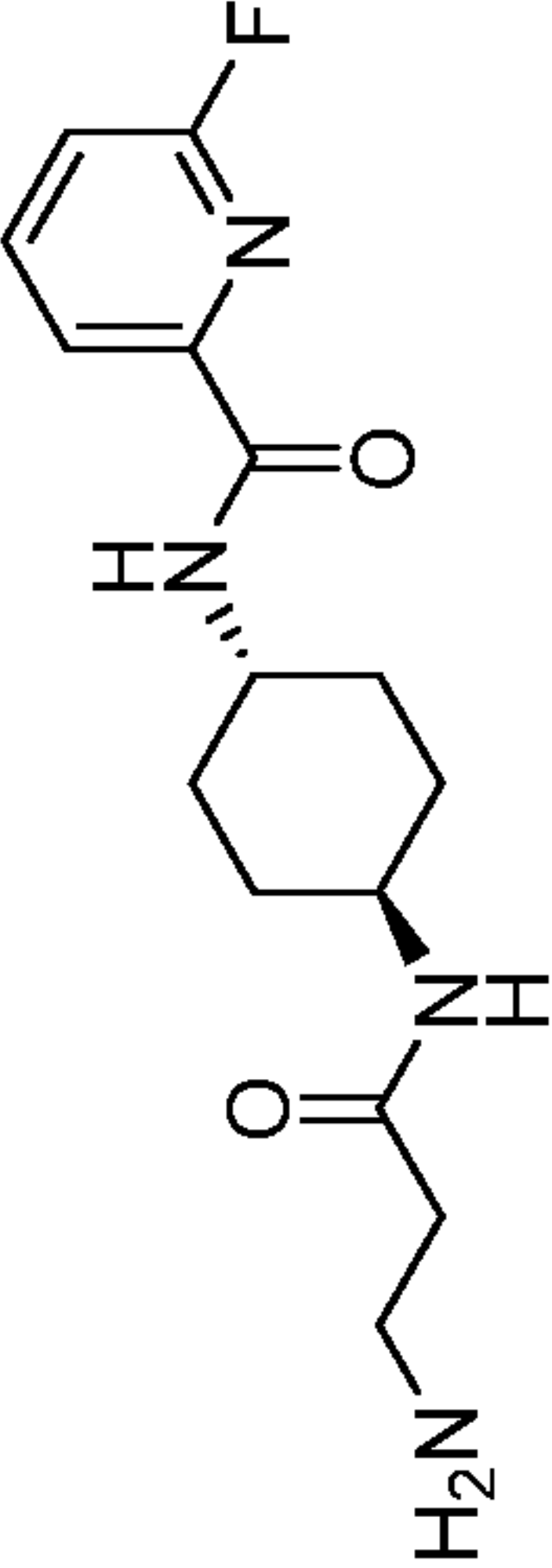
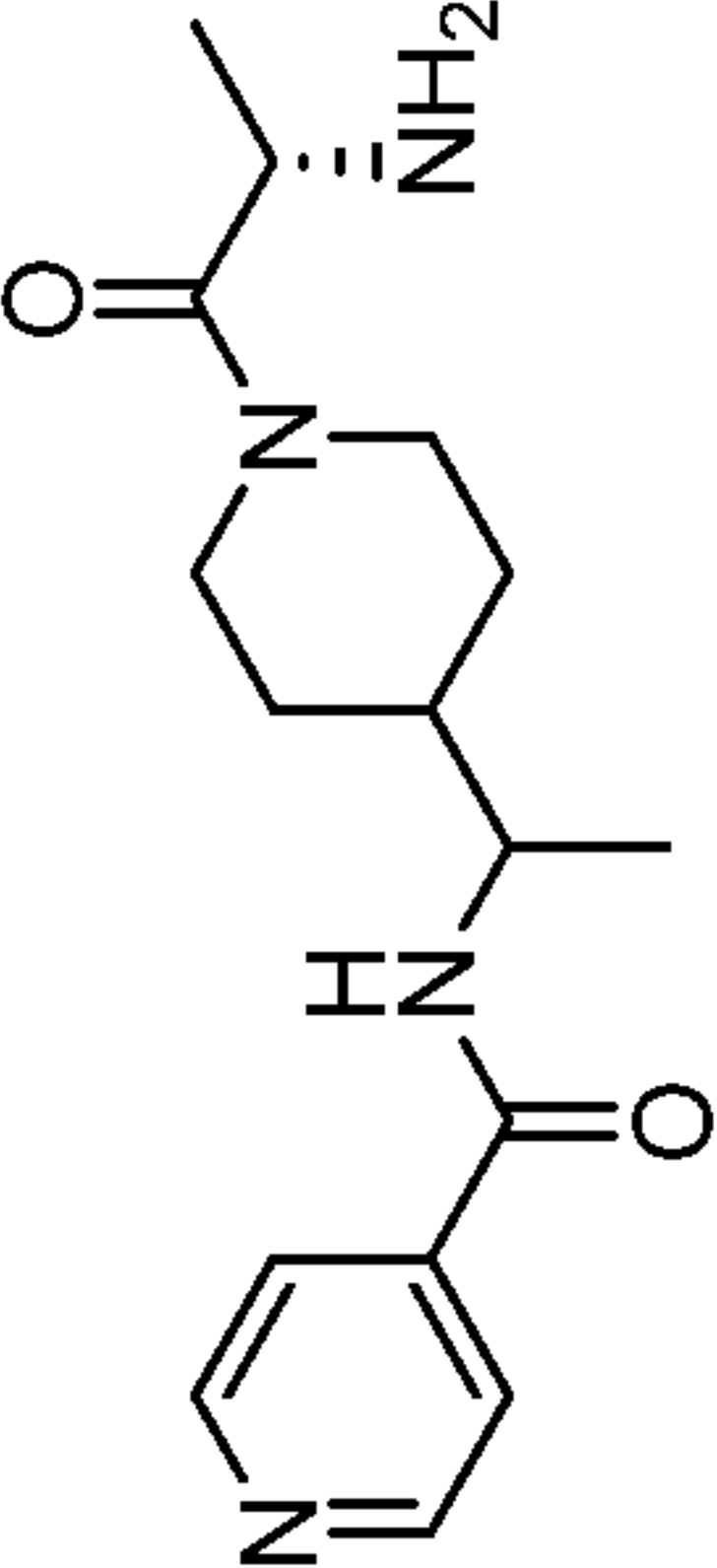
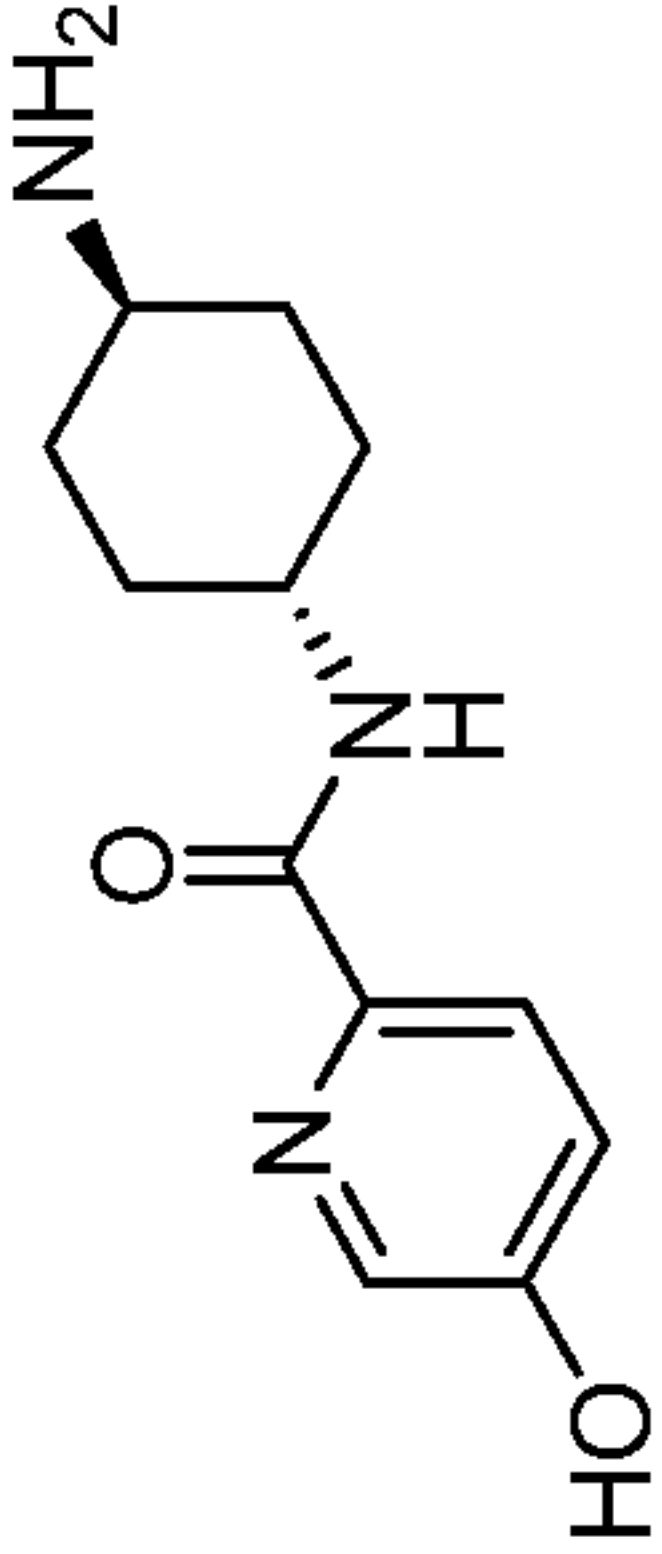
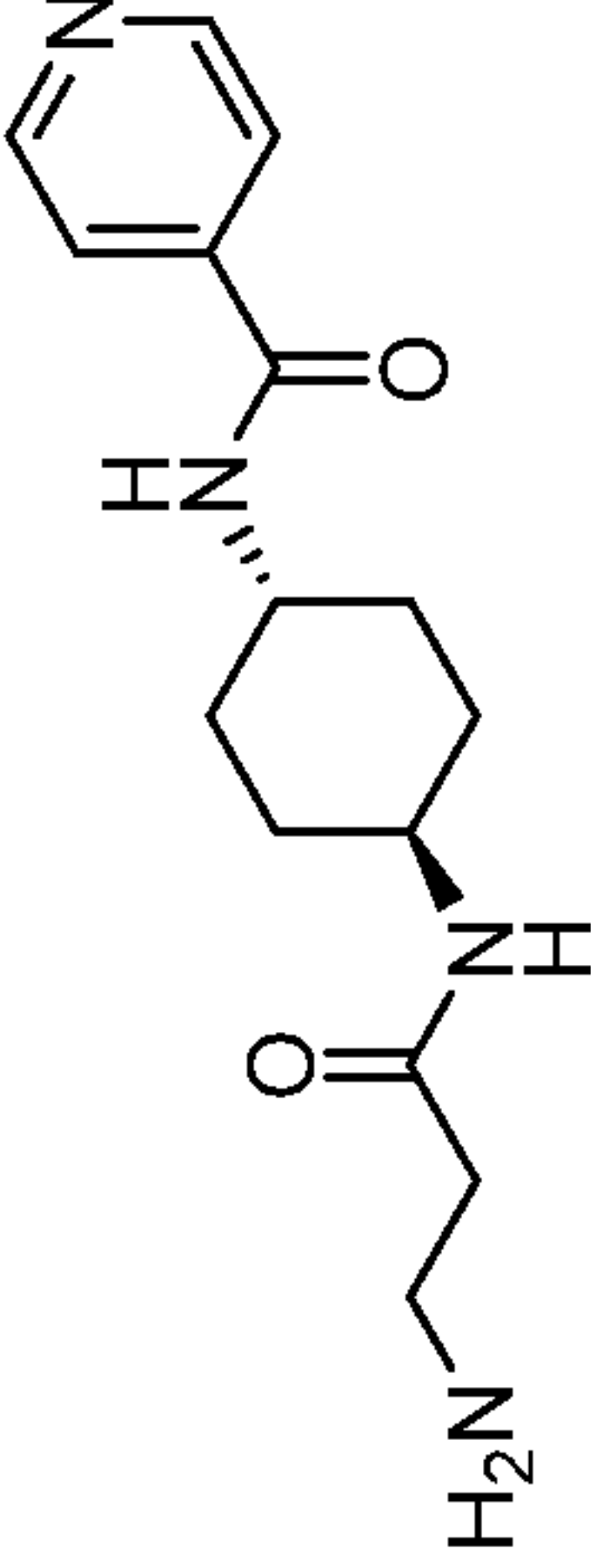
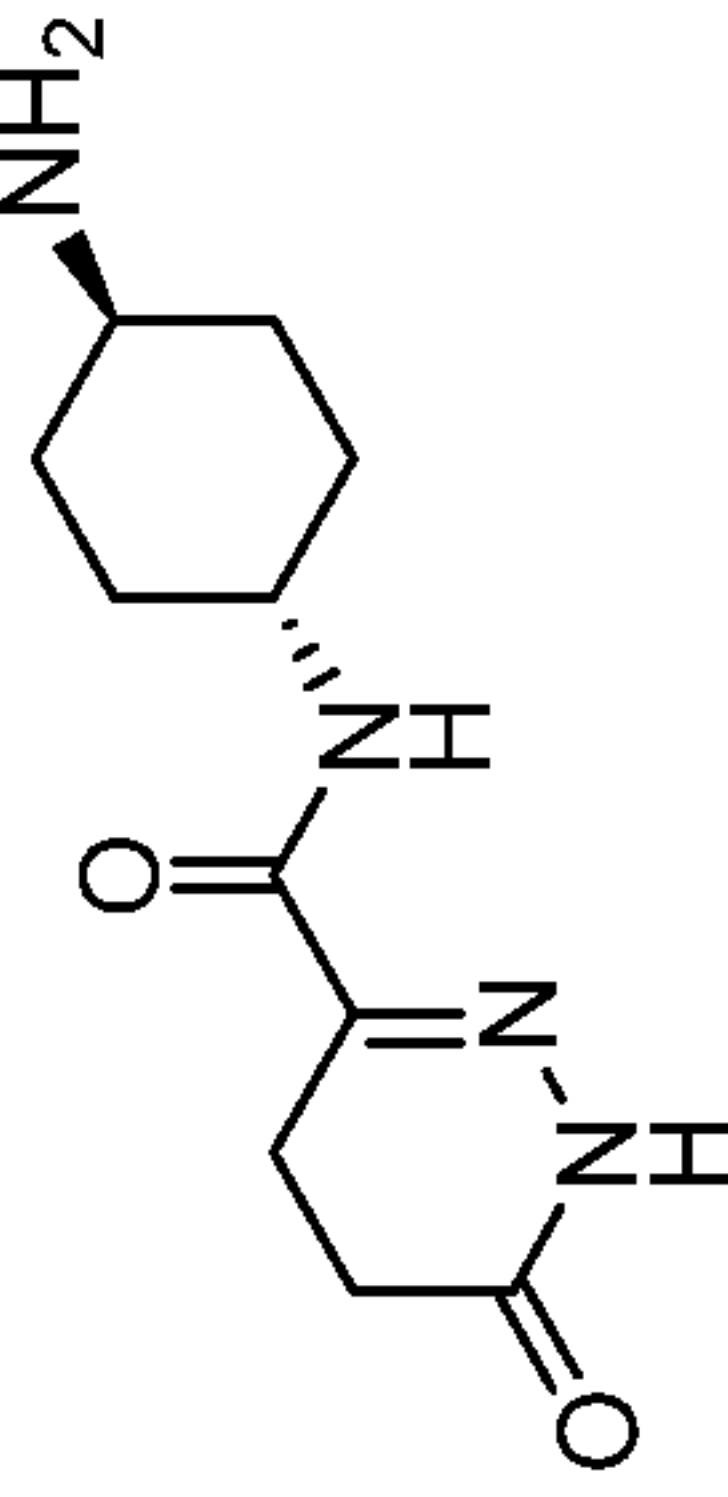
110		HCl	397		TFA
111		HCl	398		TFA
112		TFA	399		HCl
113		HCl	400		HCl

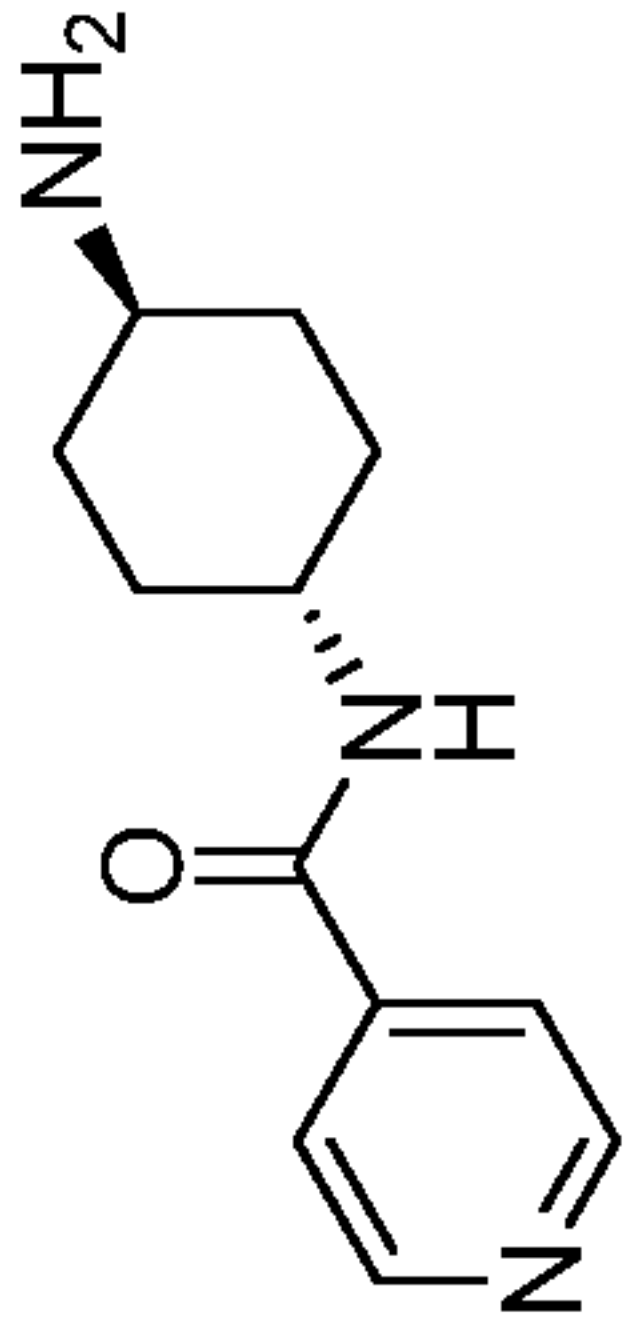
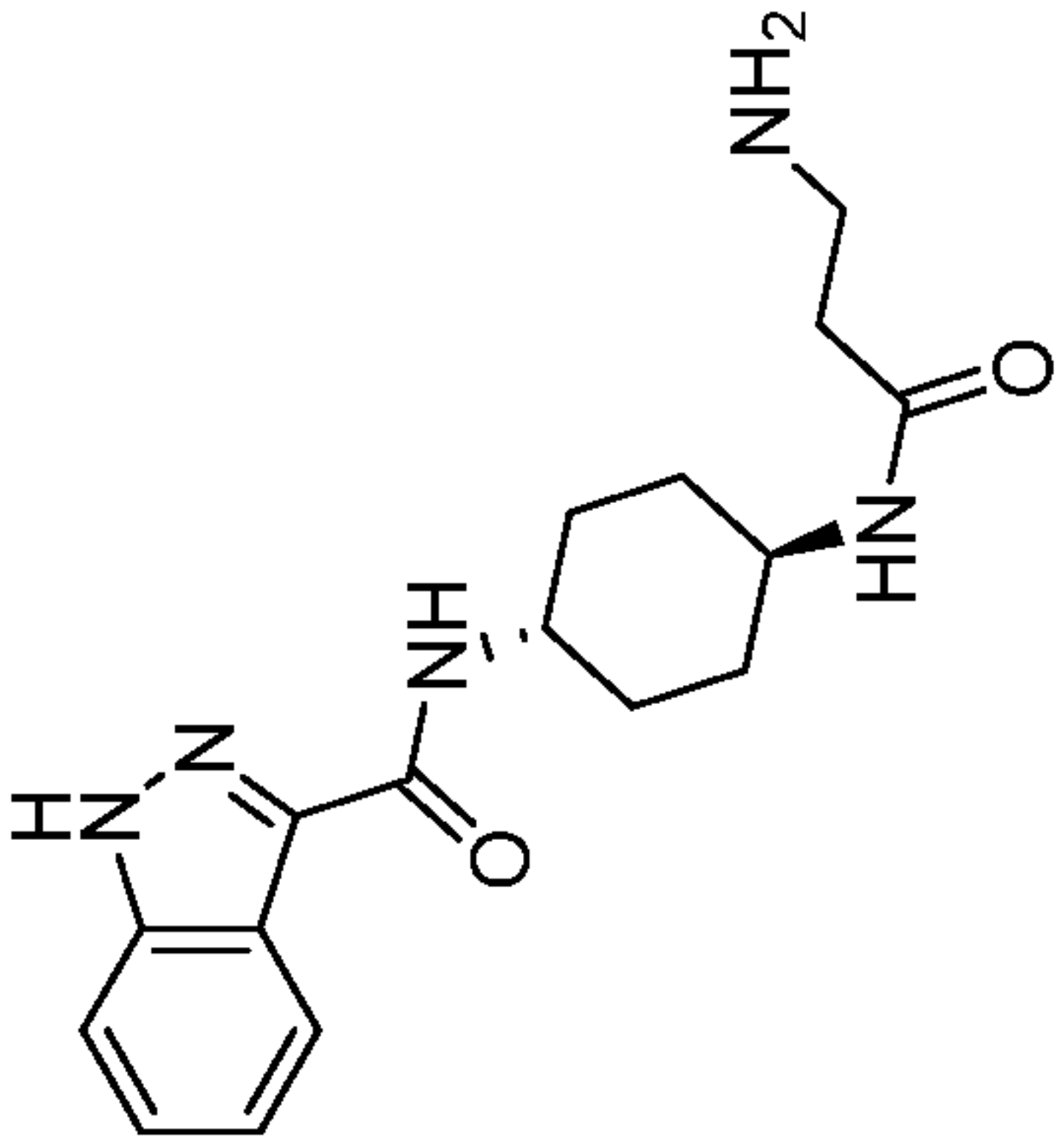
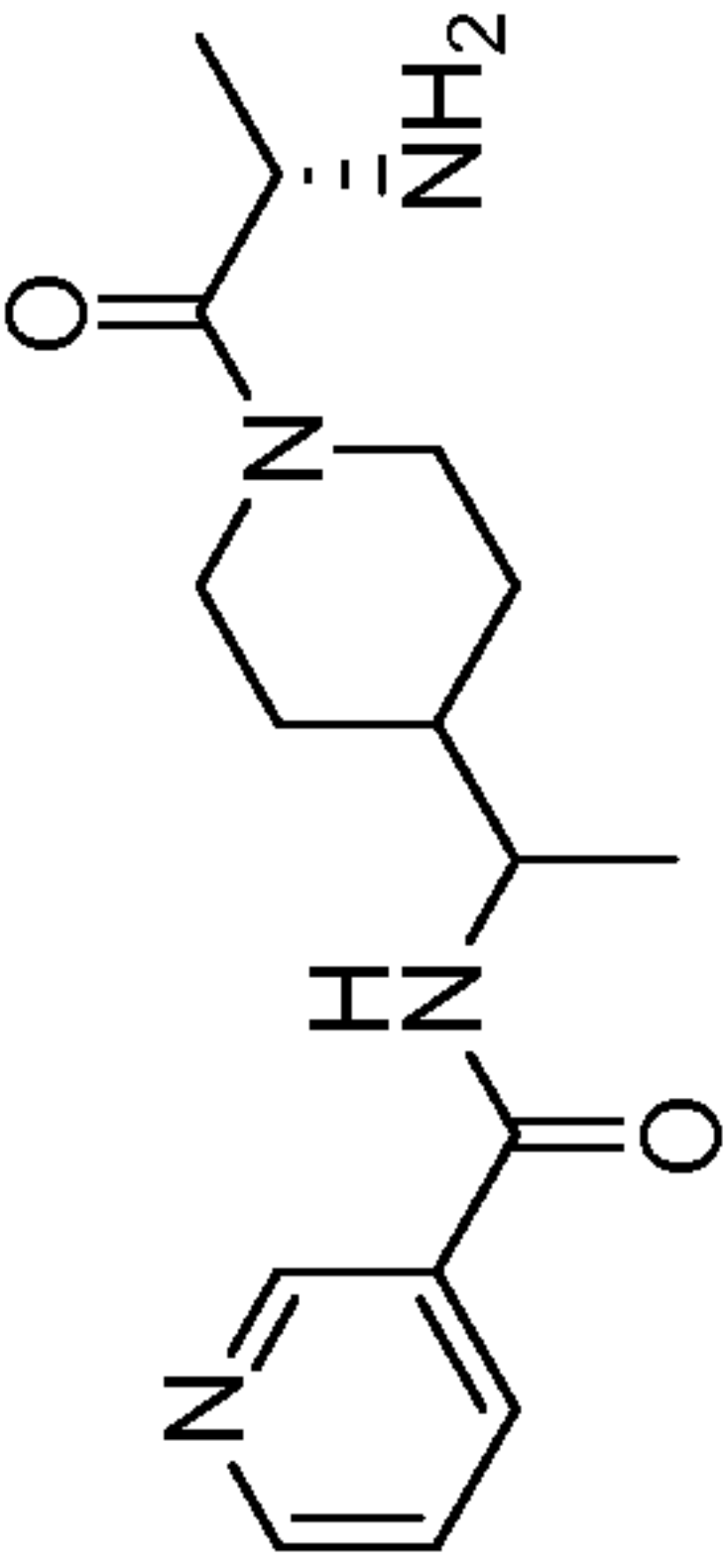
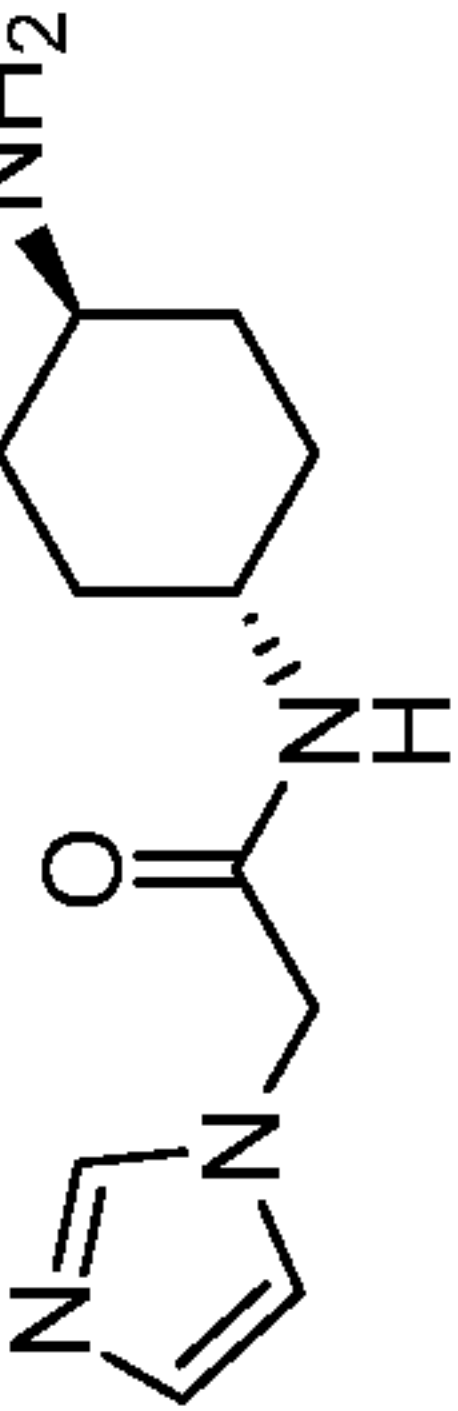
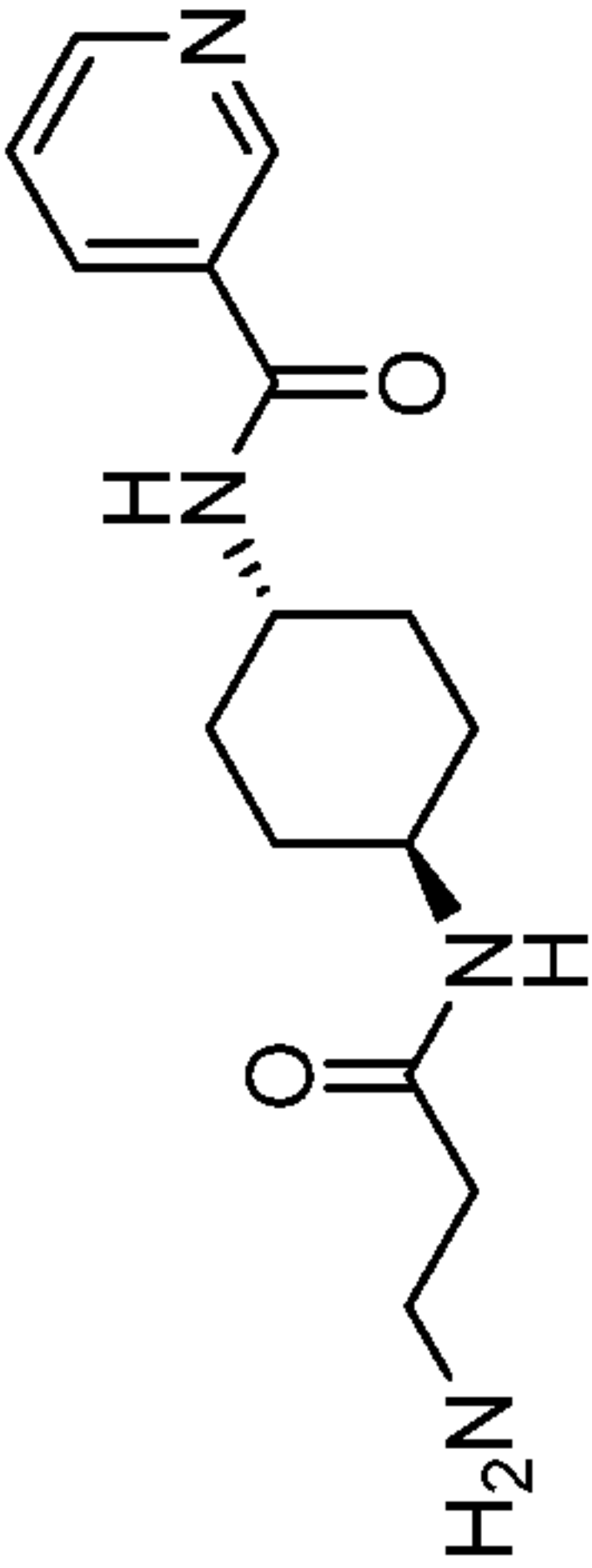
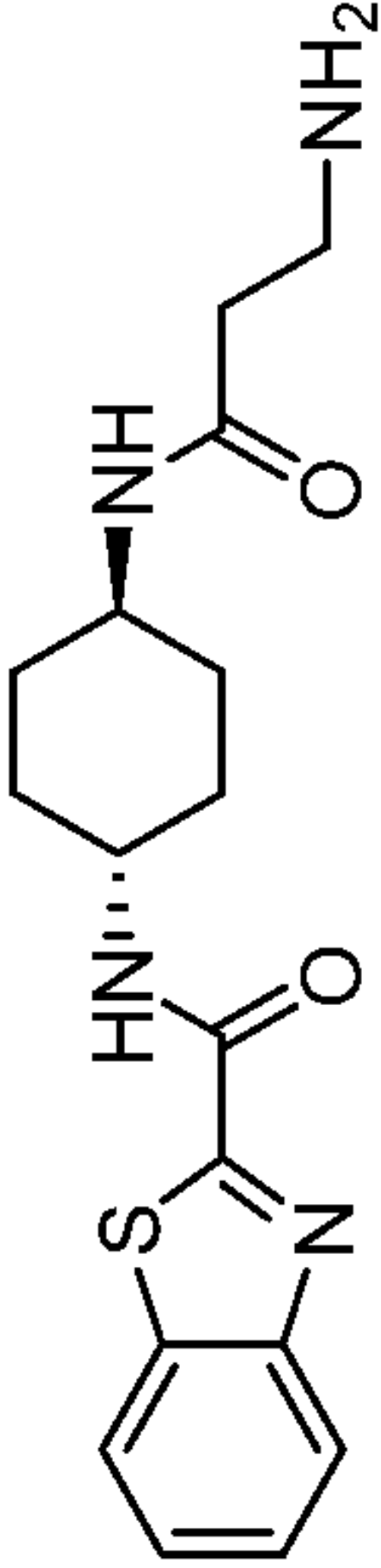
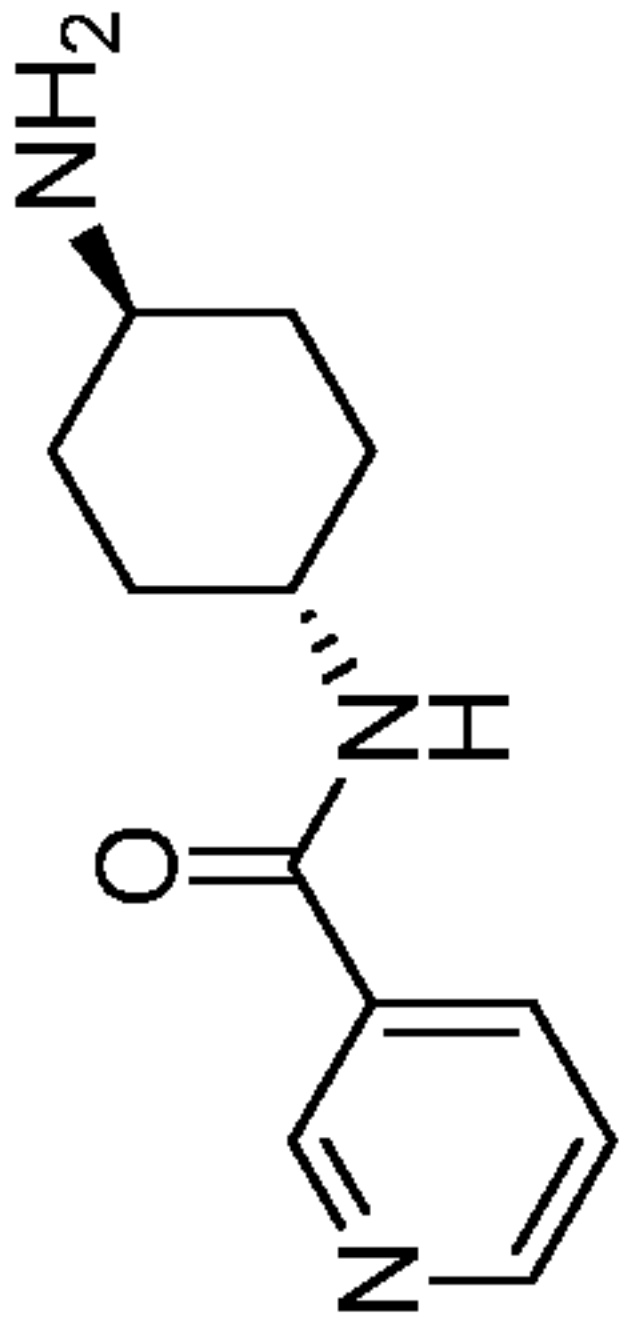
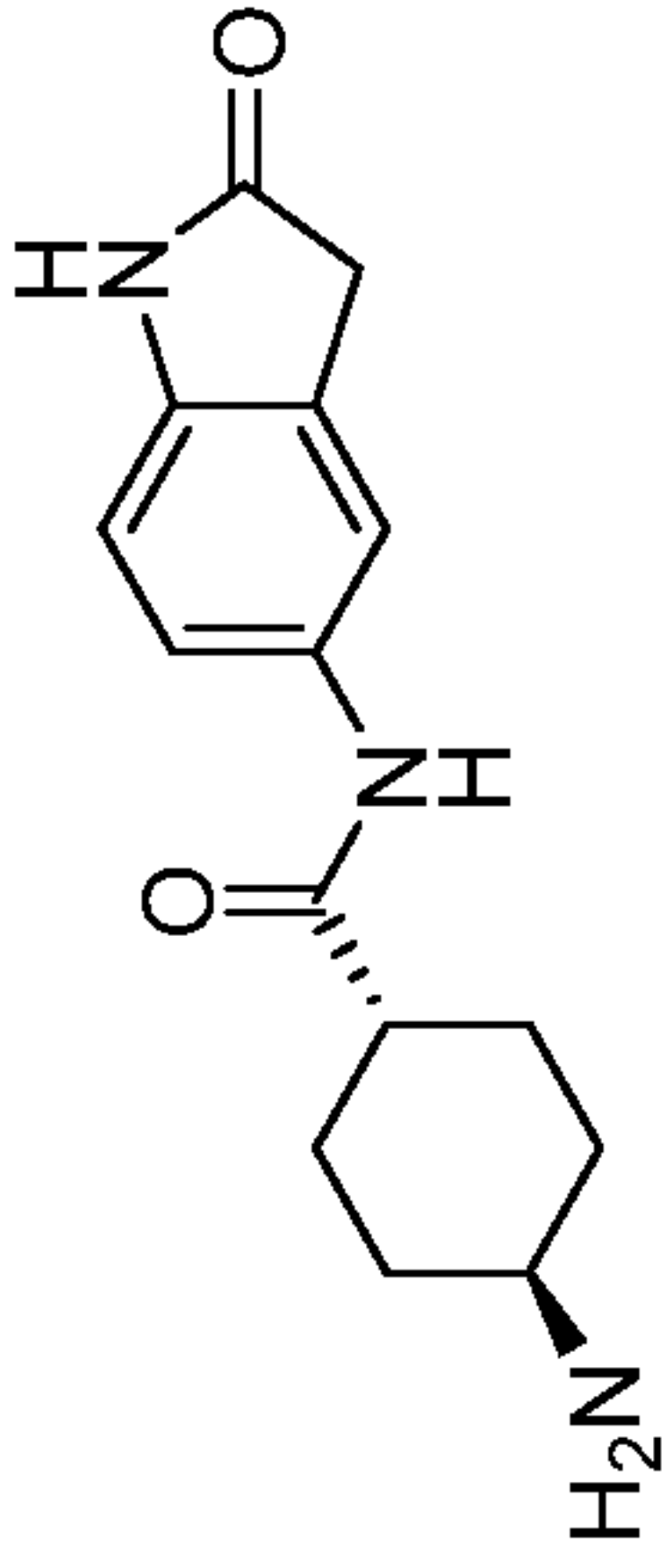
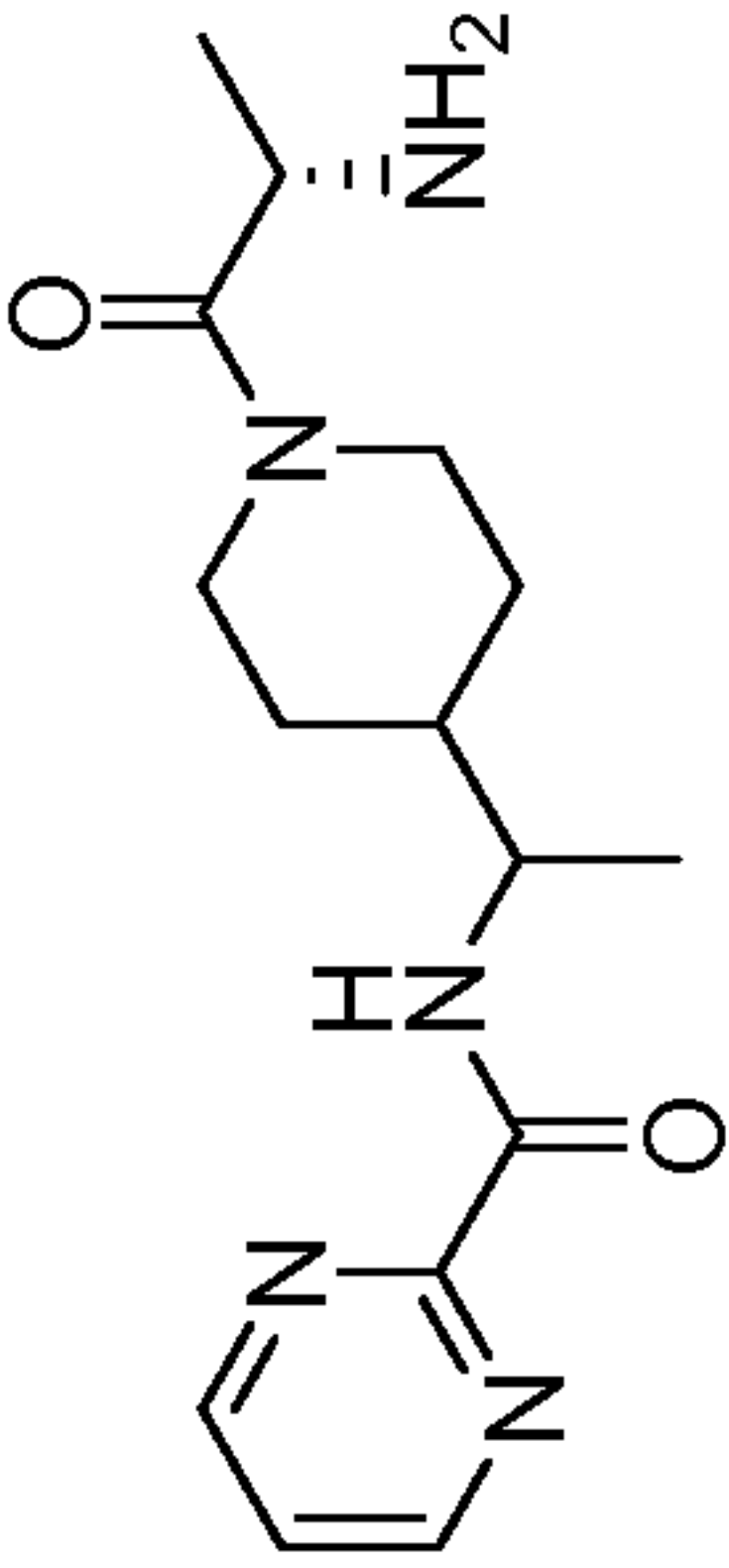
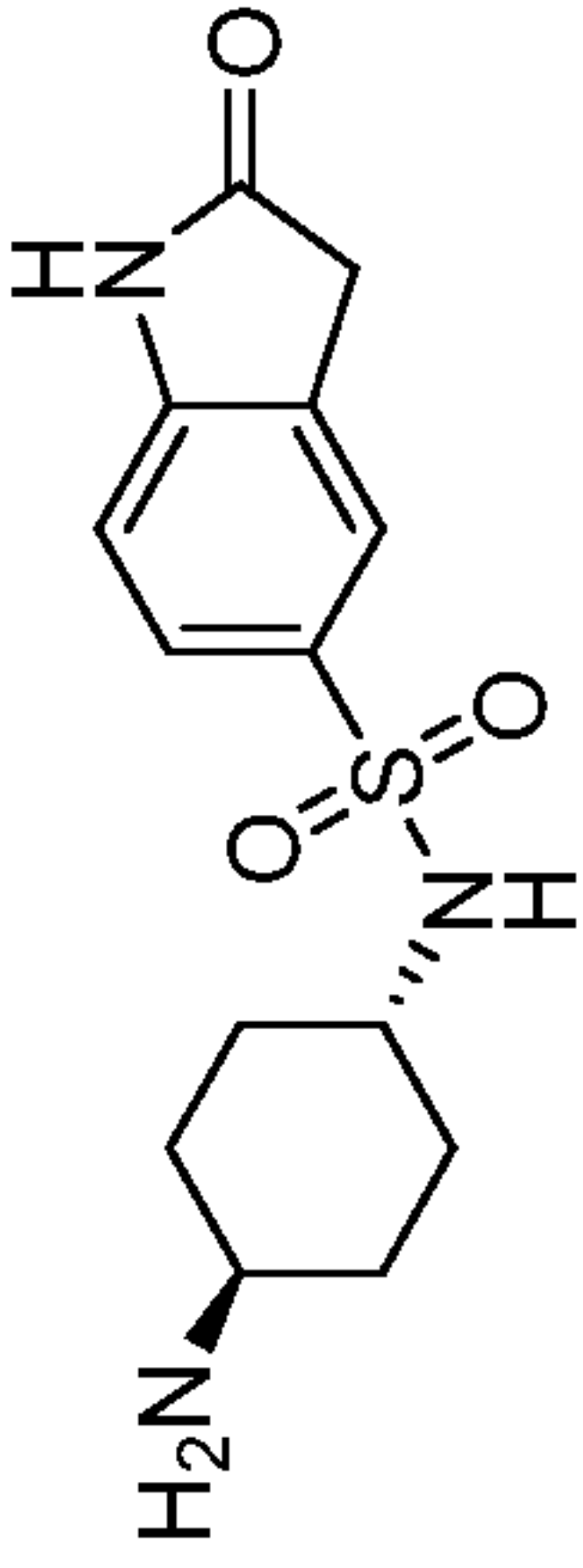
114		TFA	401		TFA
115		TFA	402		TFA
116		TFA	403		TFA
117		TFA	404		None

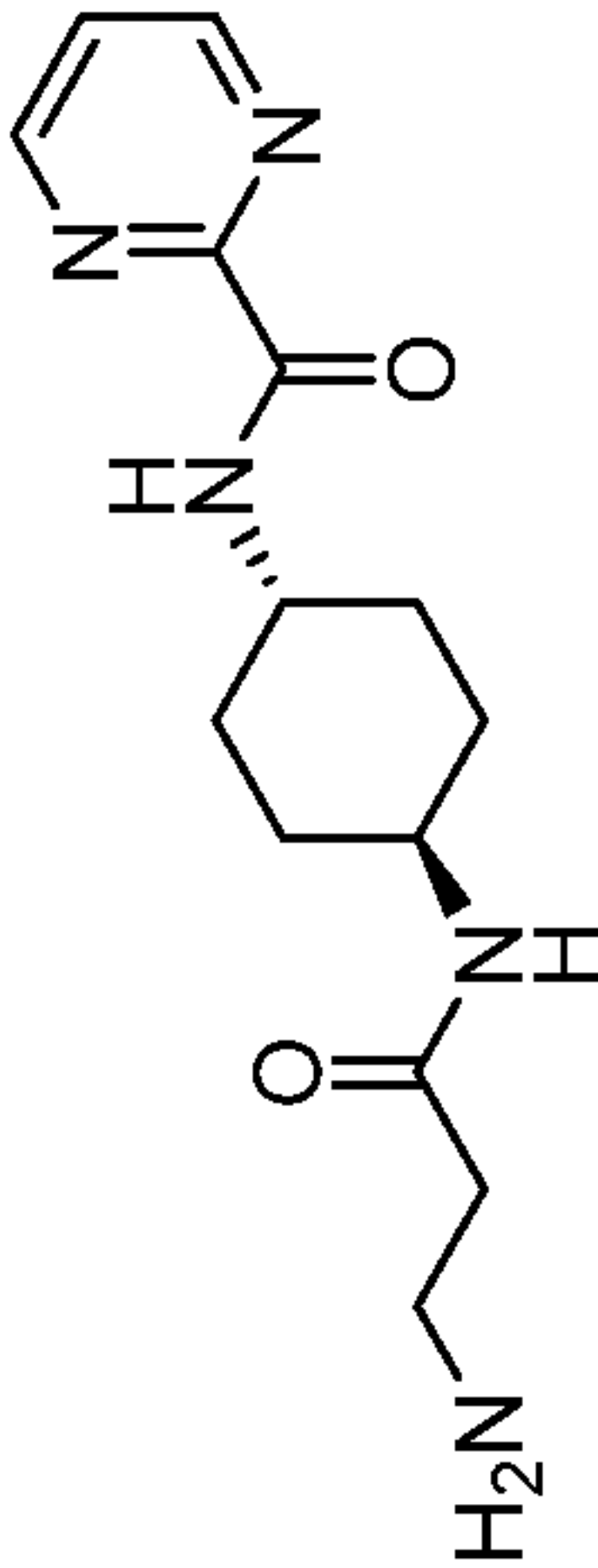
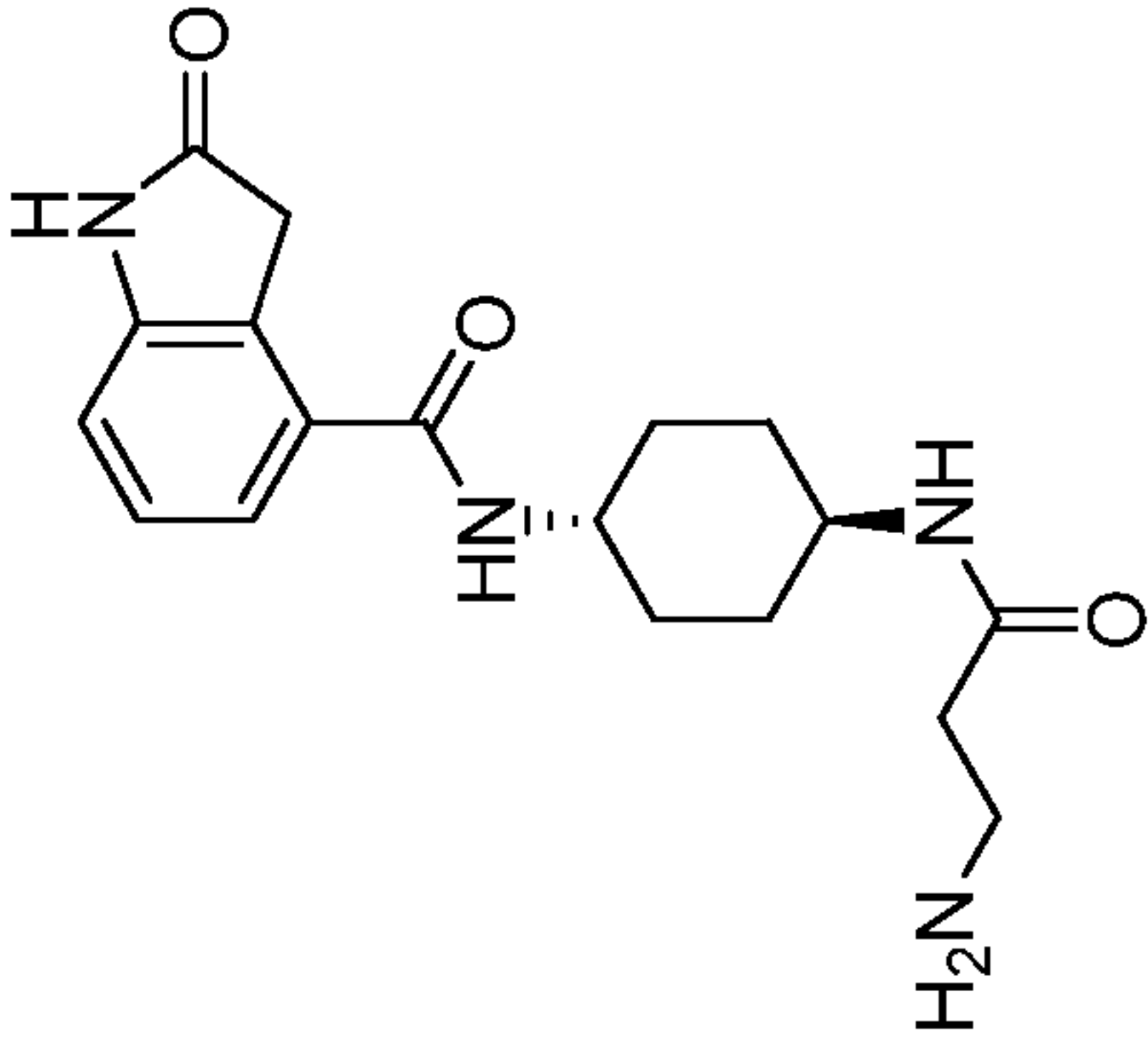
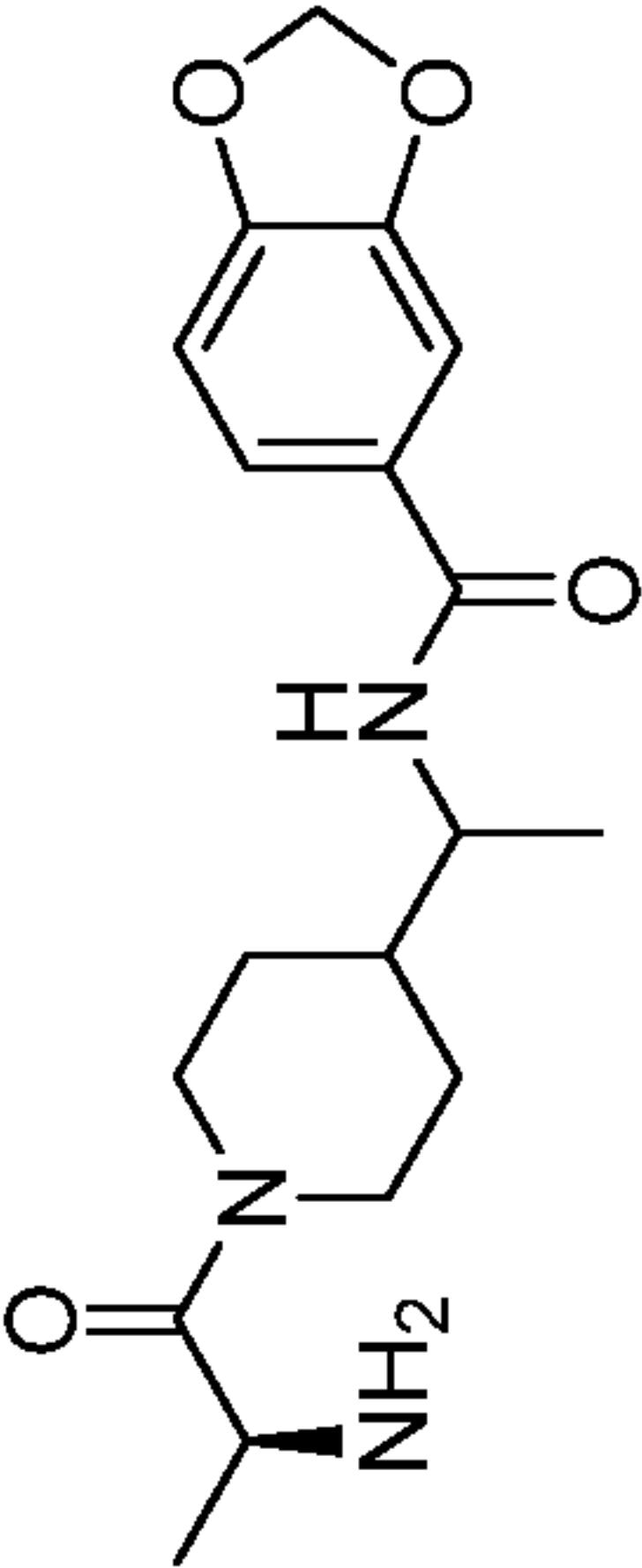
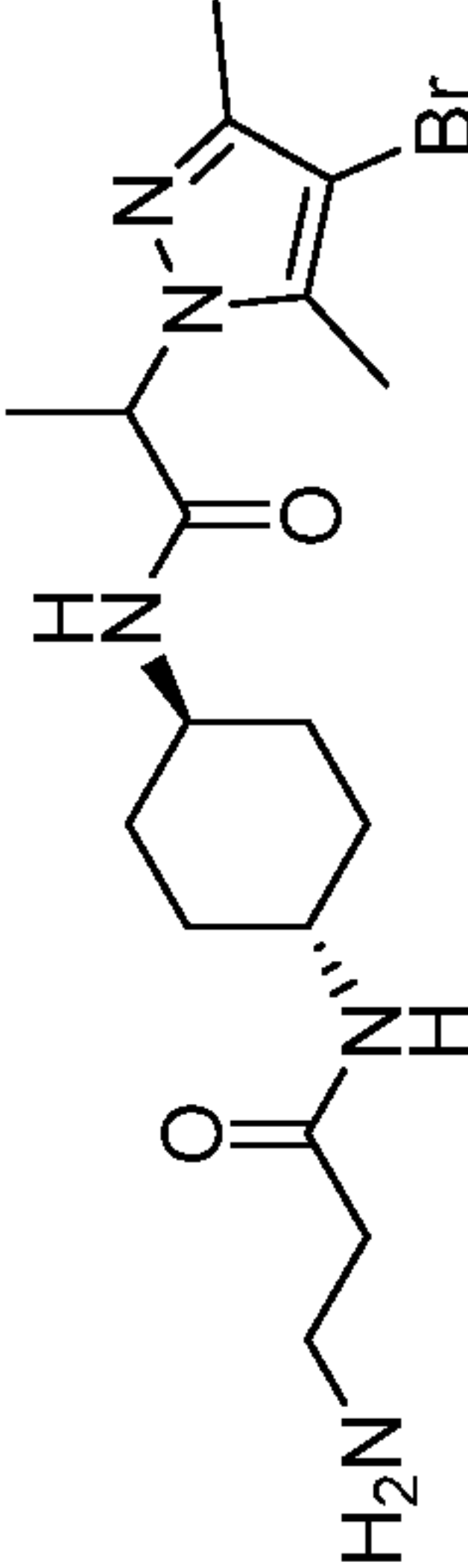
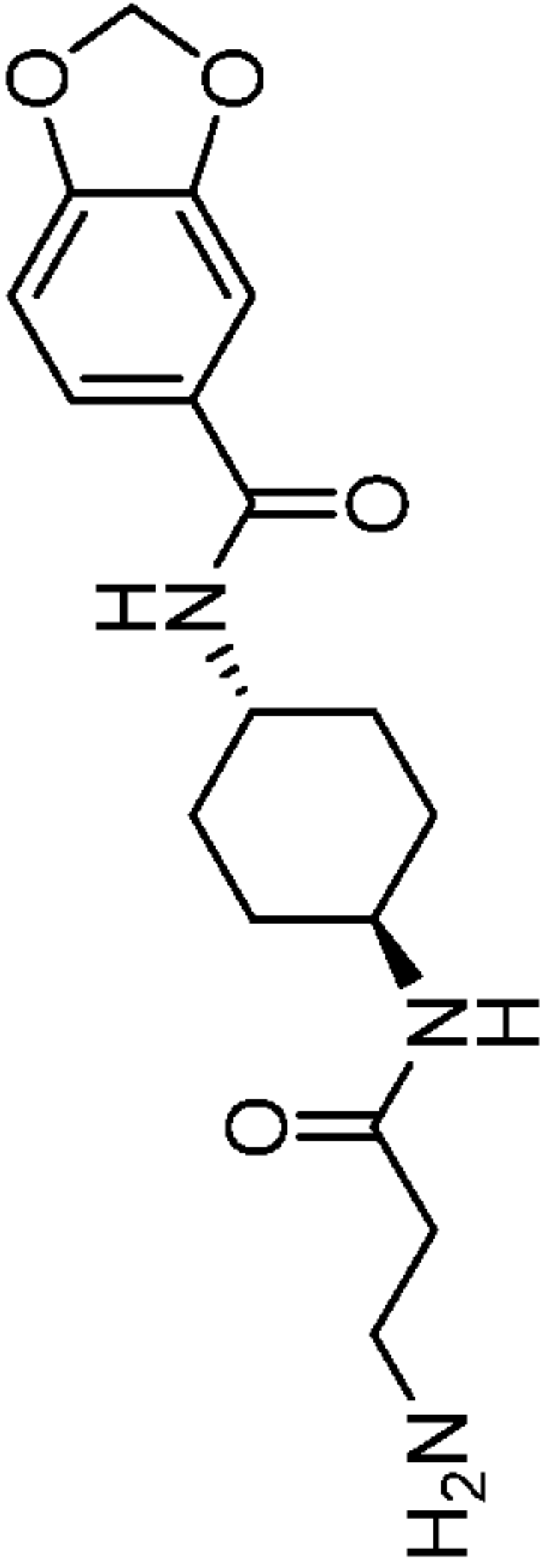
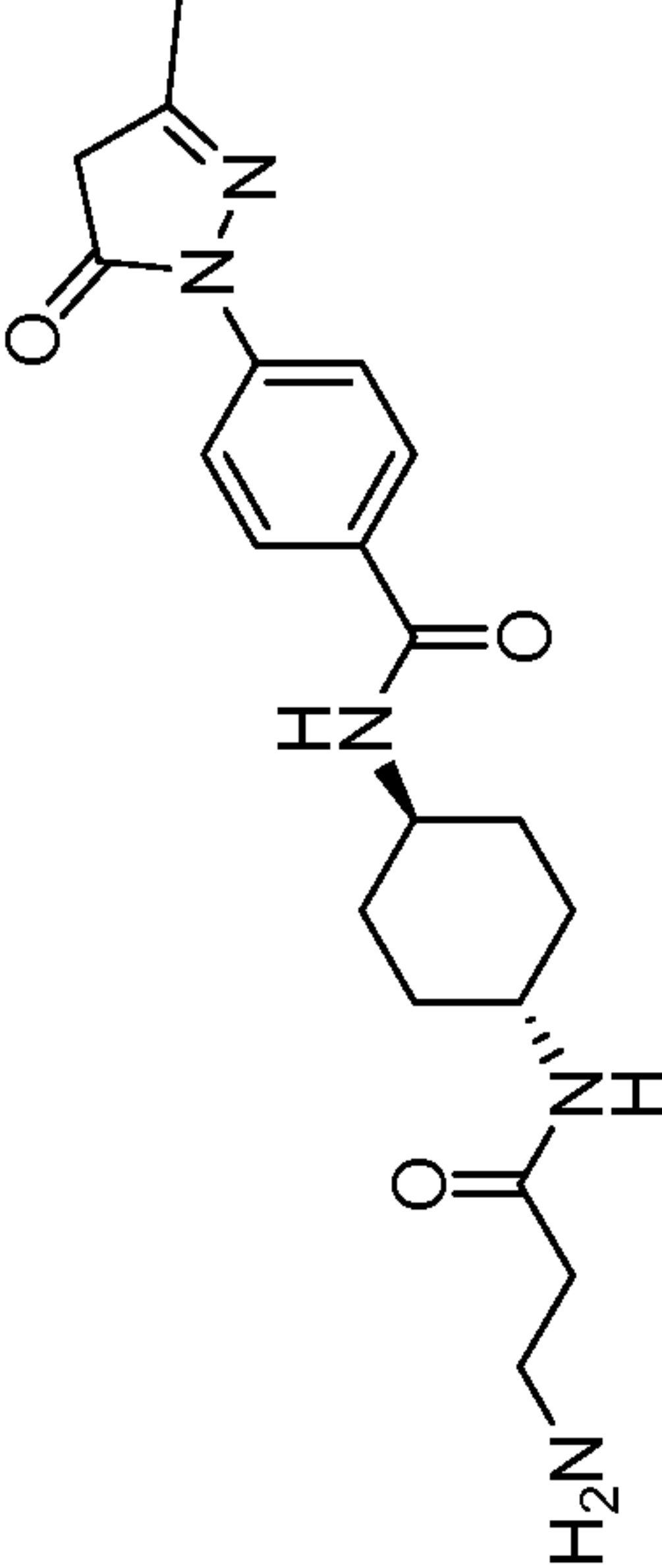
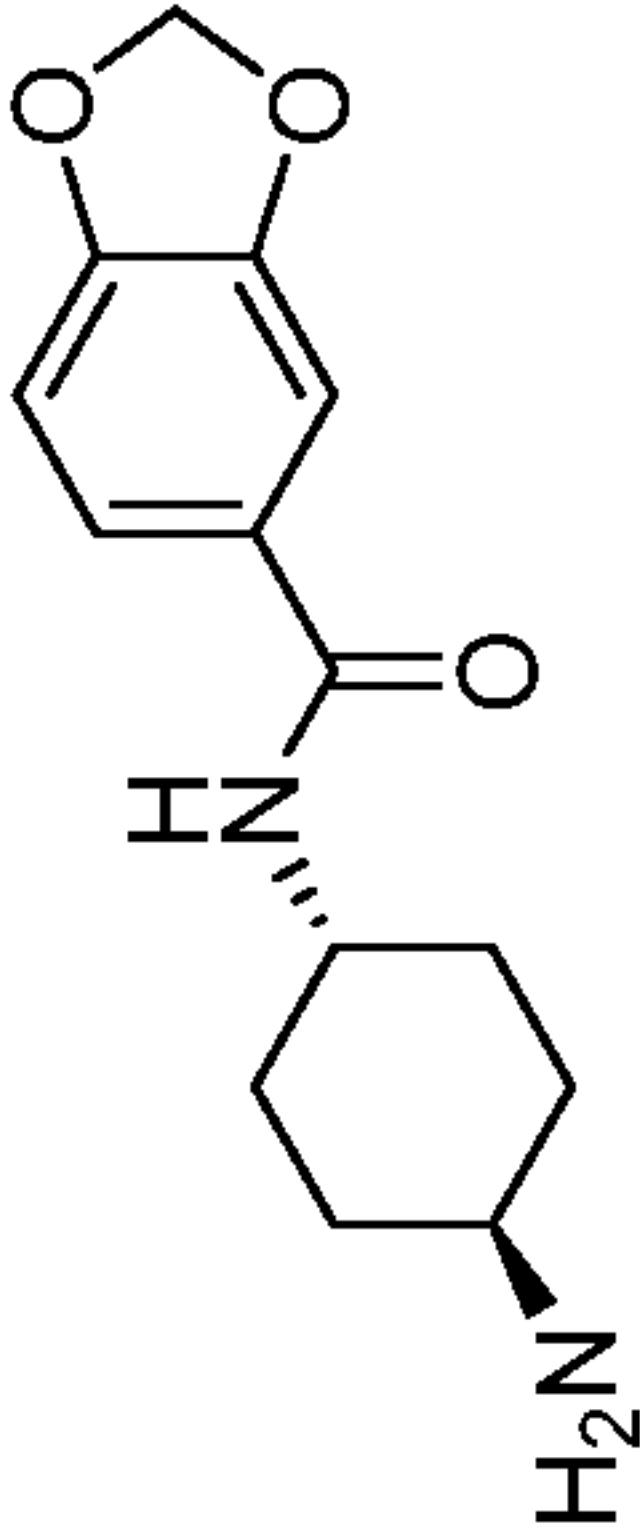
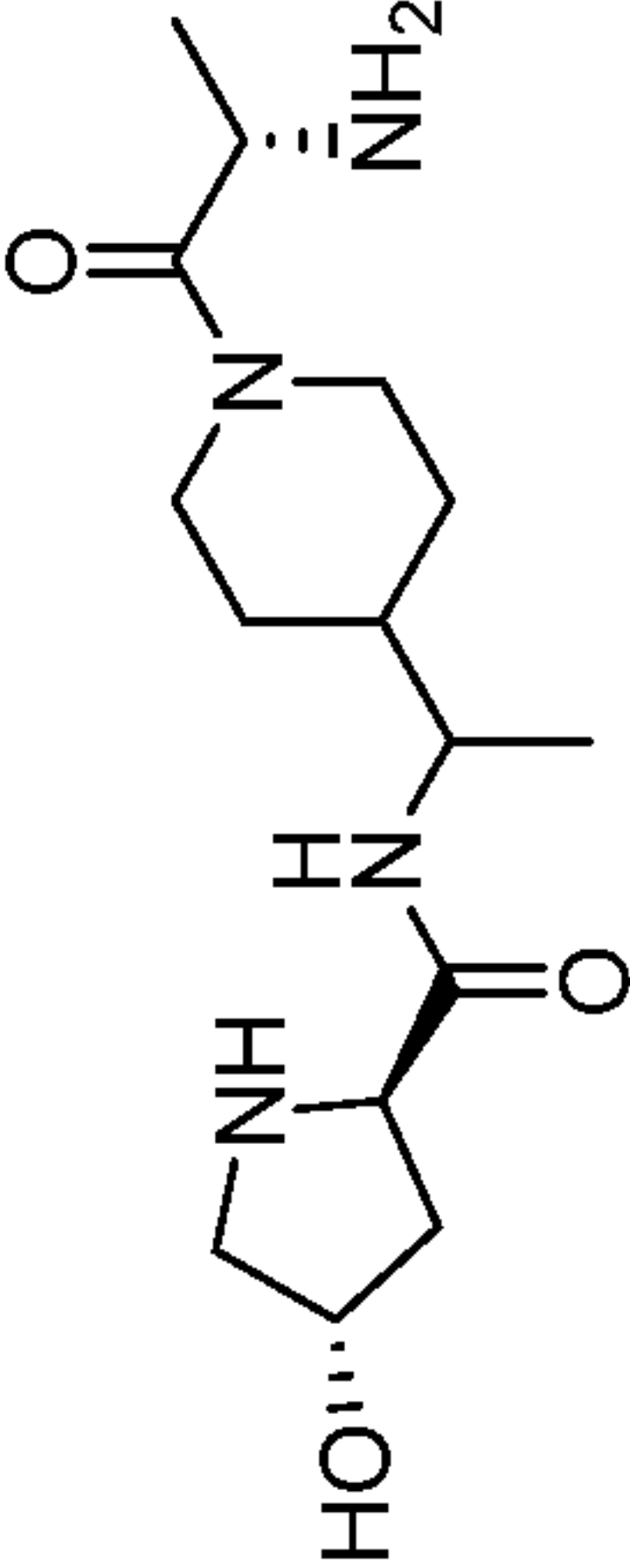
118		TFA	405		None
119		HCl	406		TFA
120		TFA	407		TFA
121		HCO OH	408		TFA
122		TFA	409		HCl

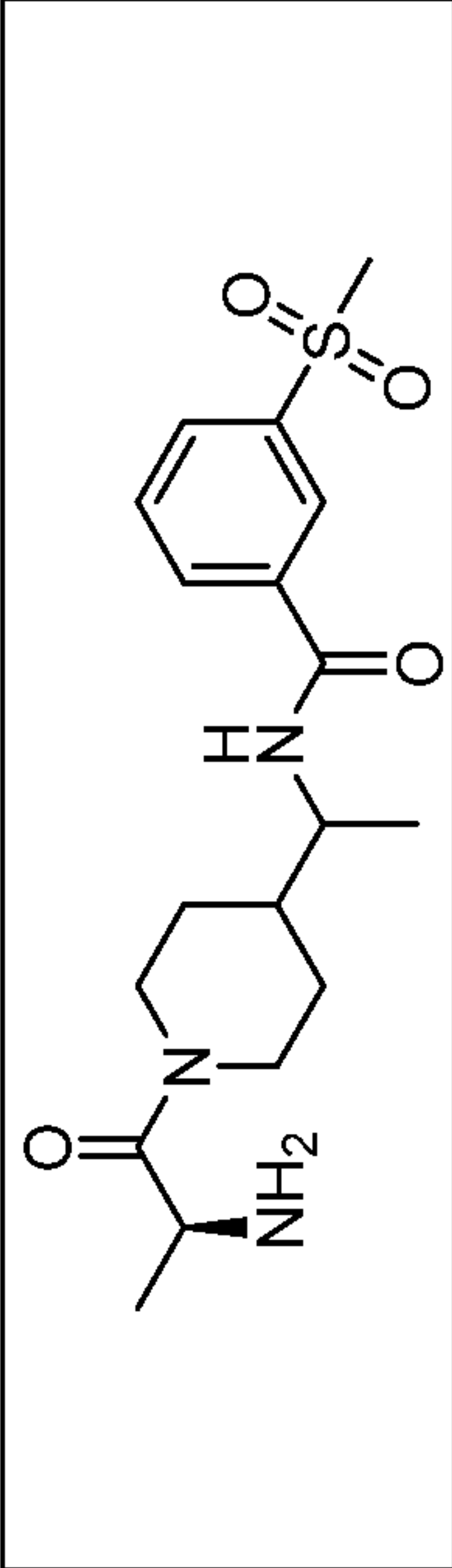
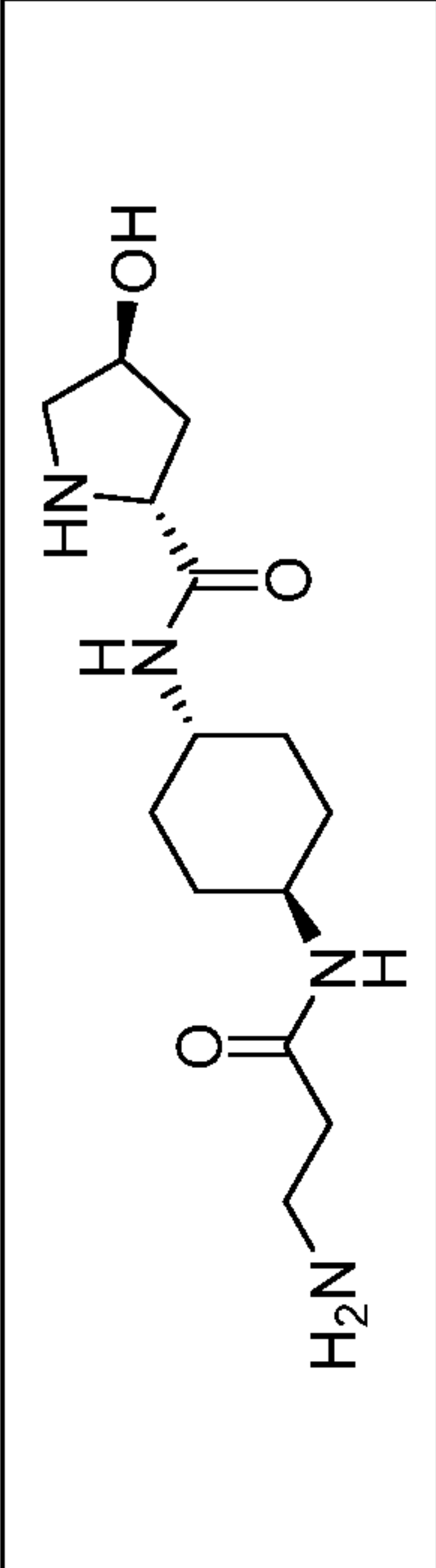
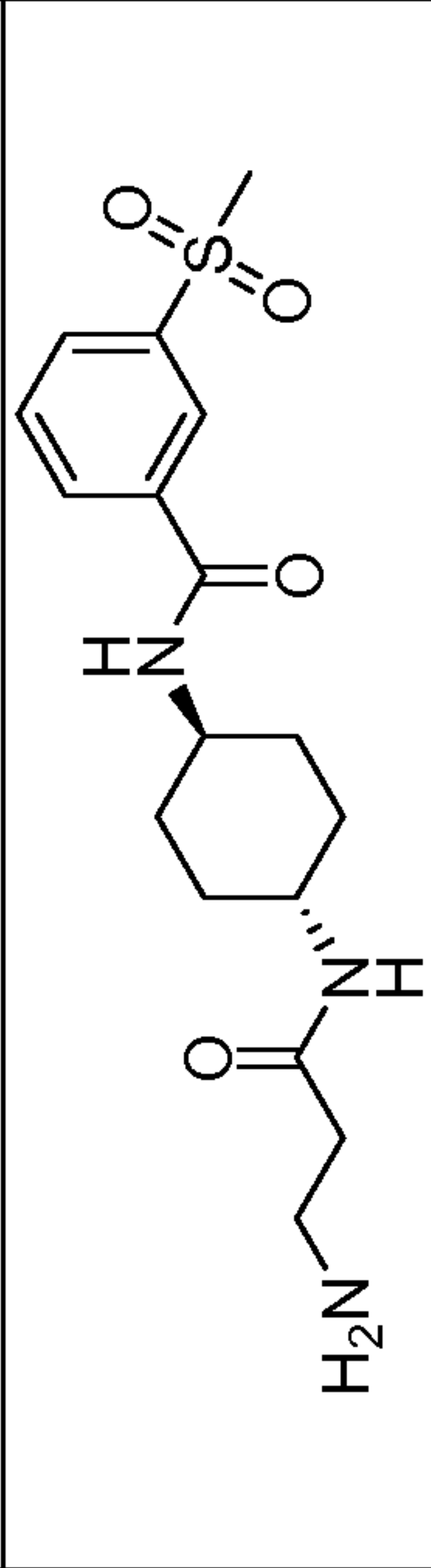
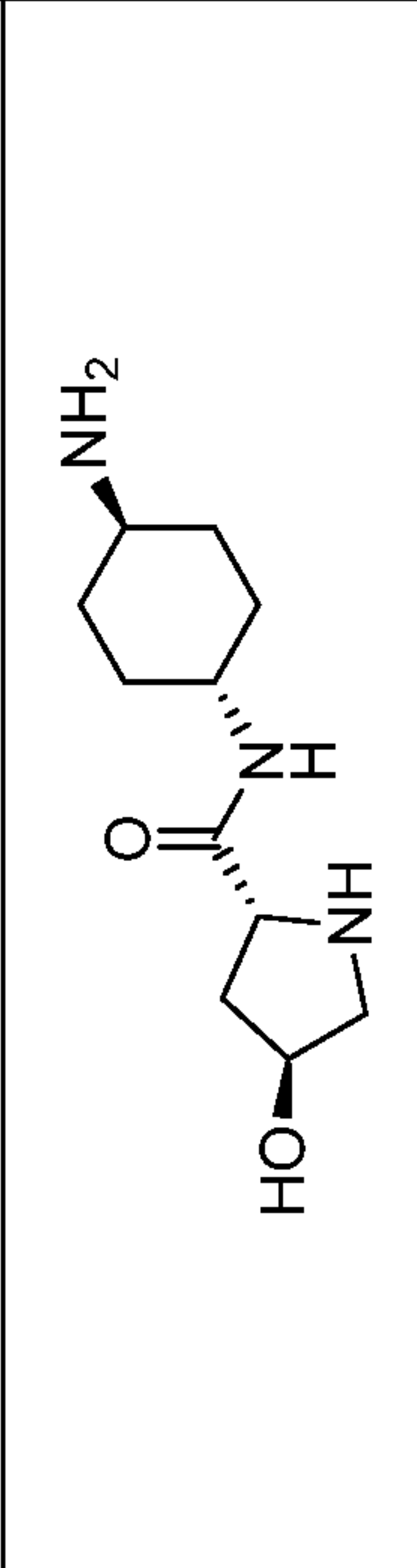
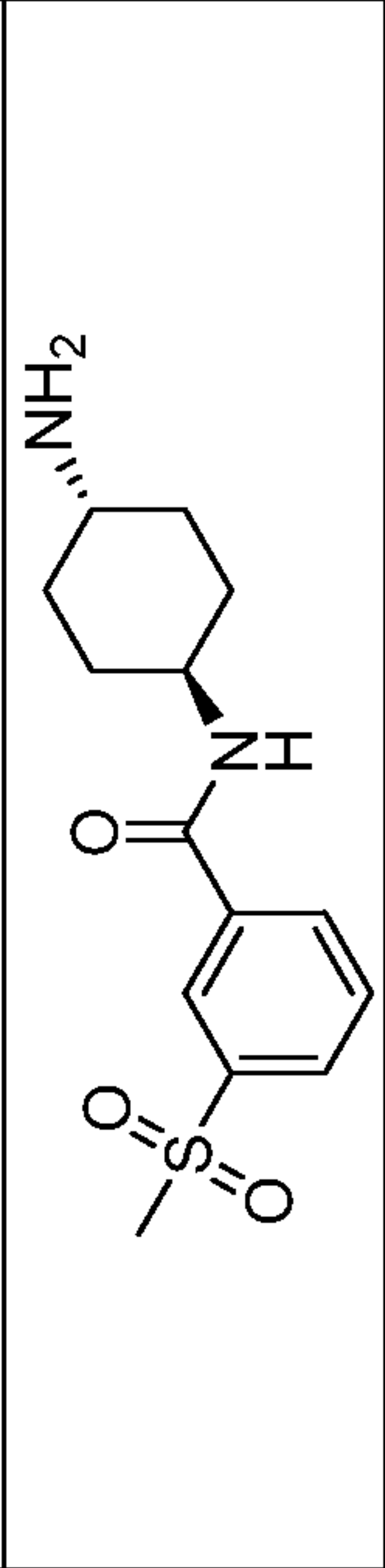
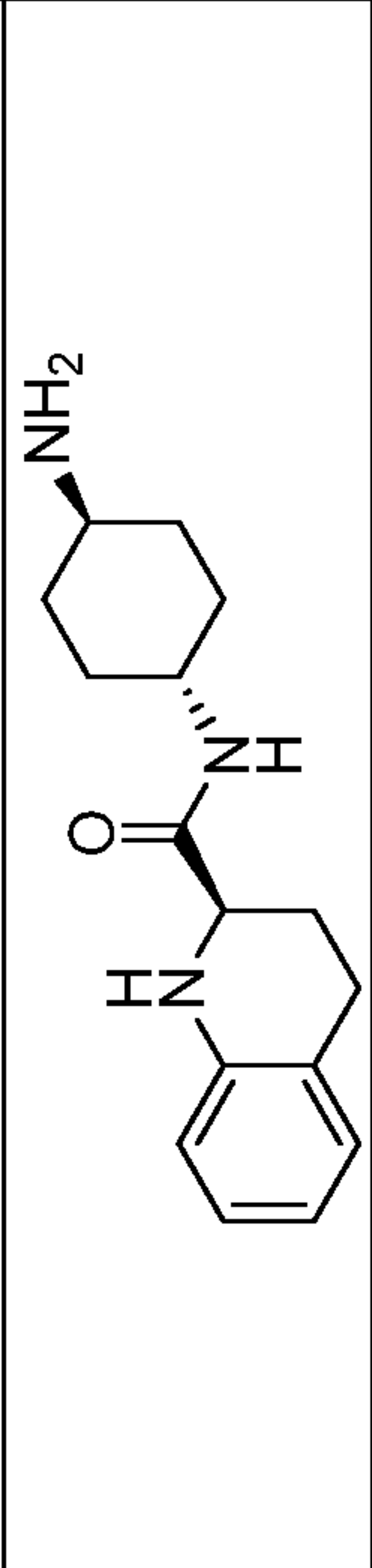
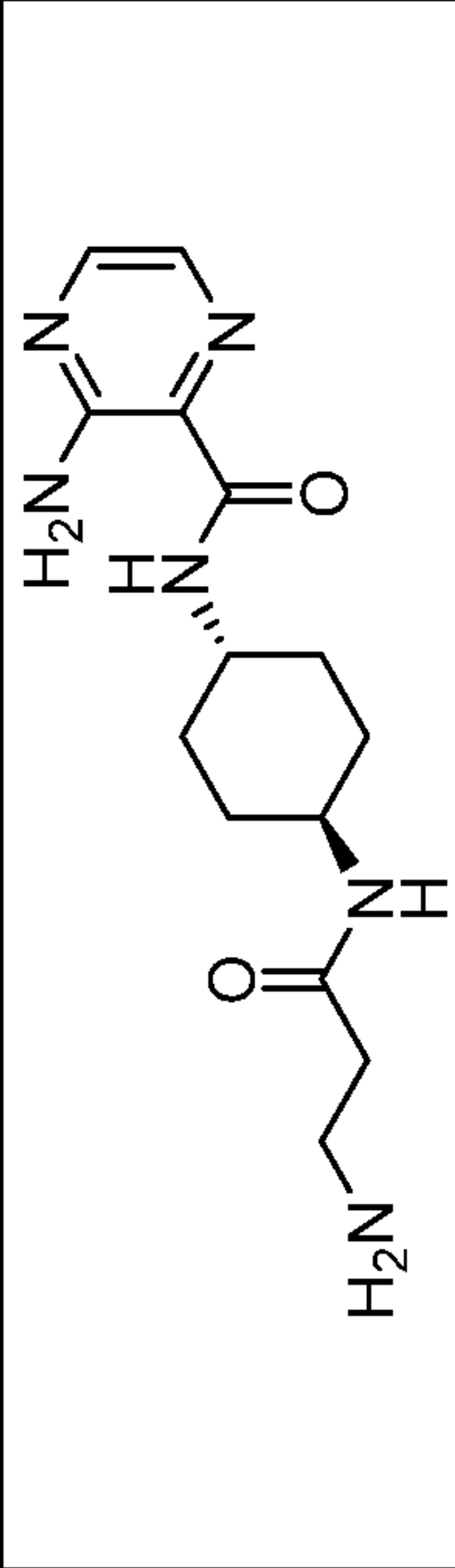
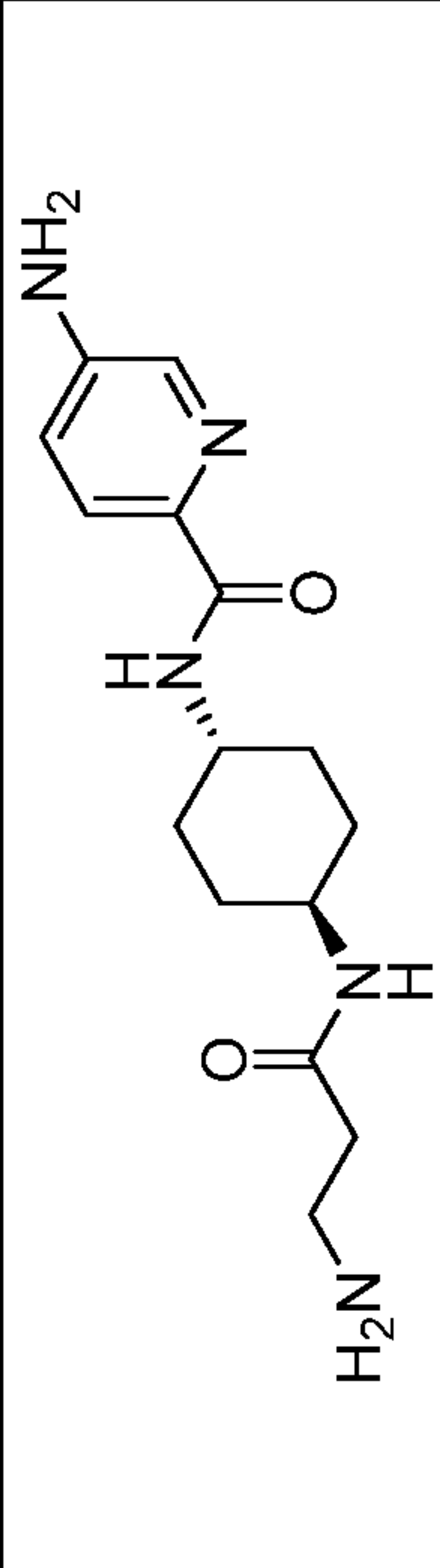
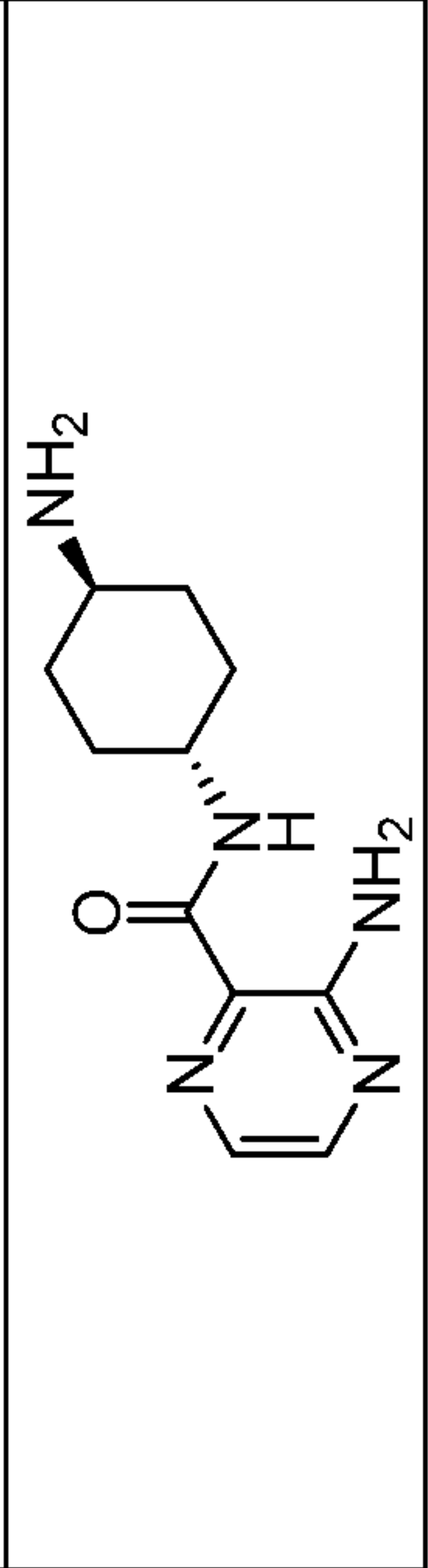
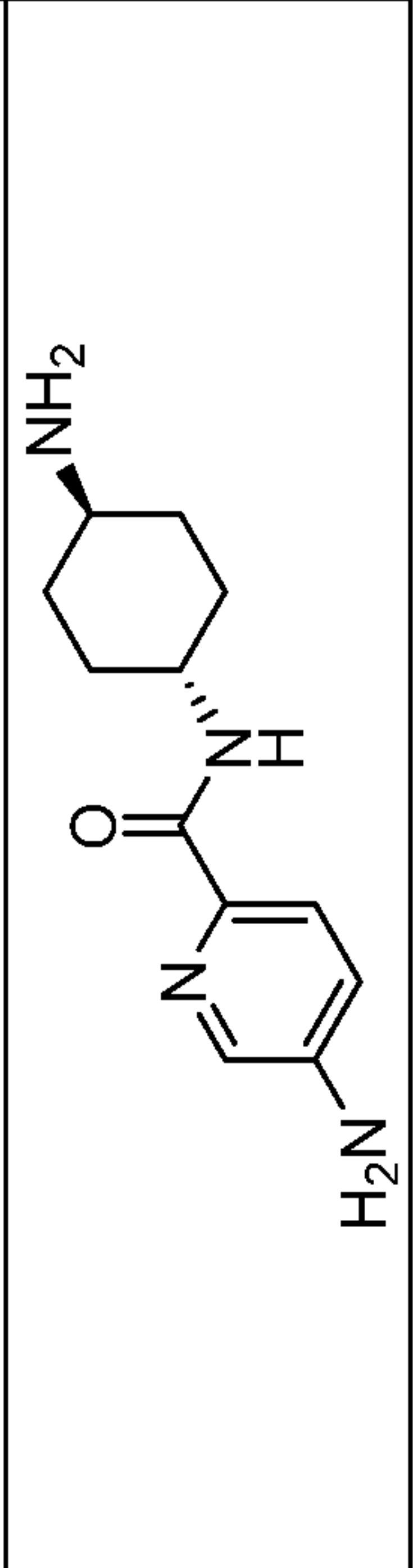
123		TFA	410		HCl
125		TFA	411		HCl
126		TFA	412		TFA
127		TFA	413		TFA
129		TFA	414		TFA

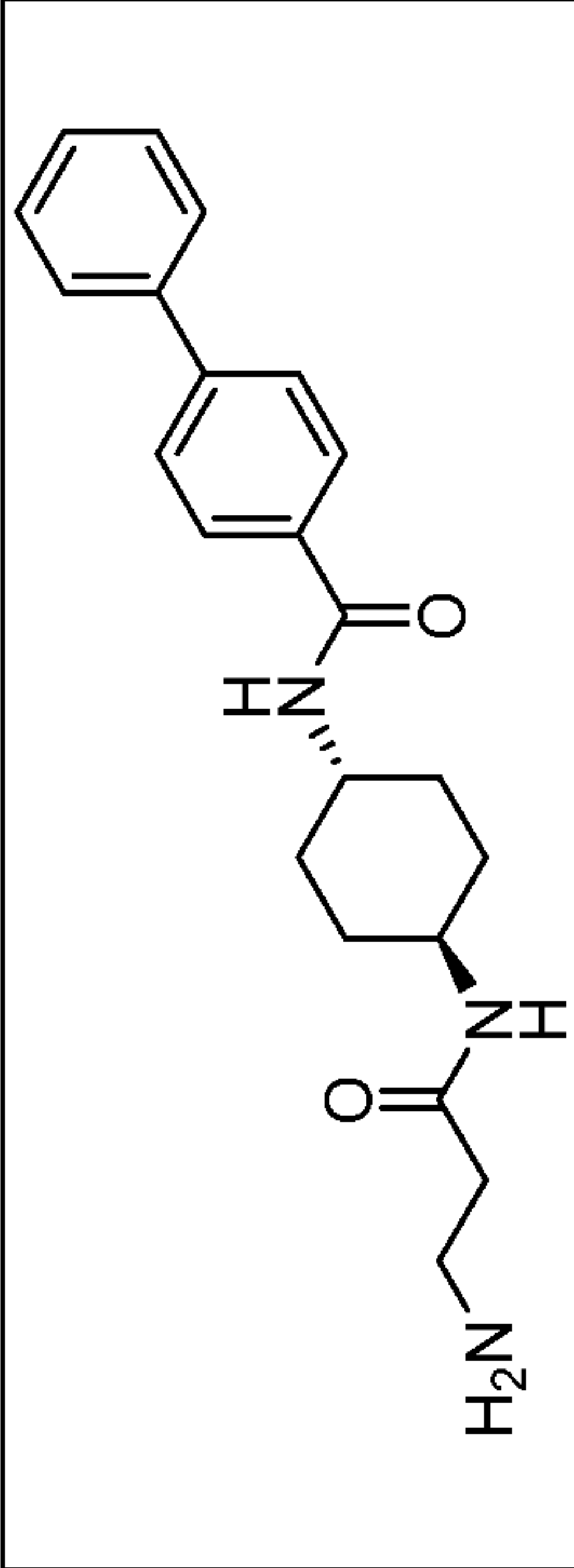
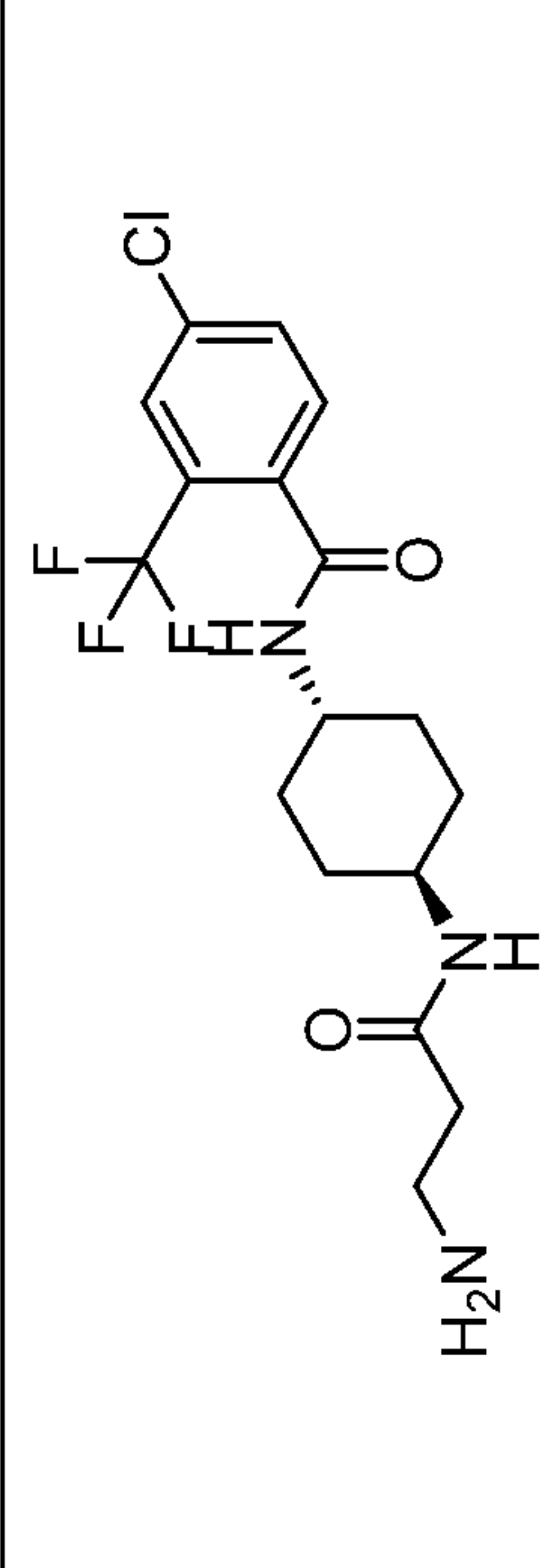
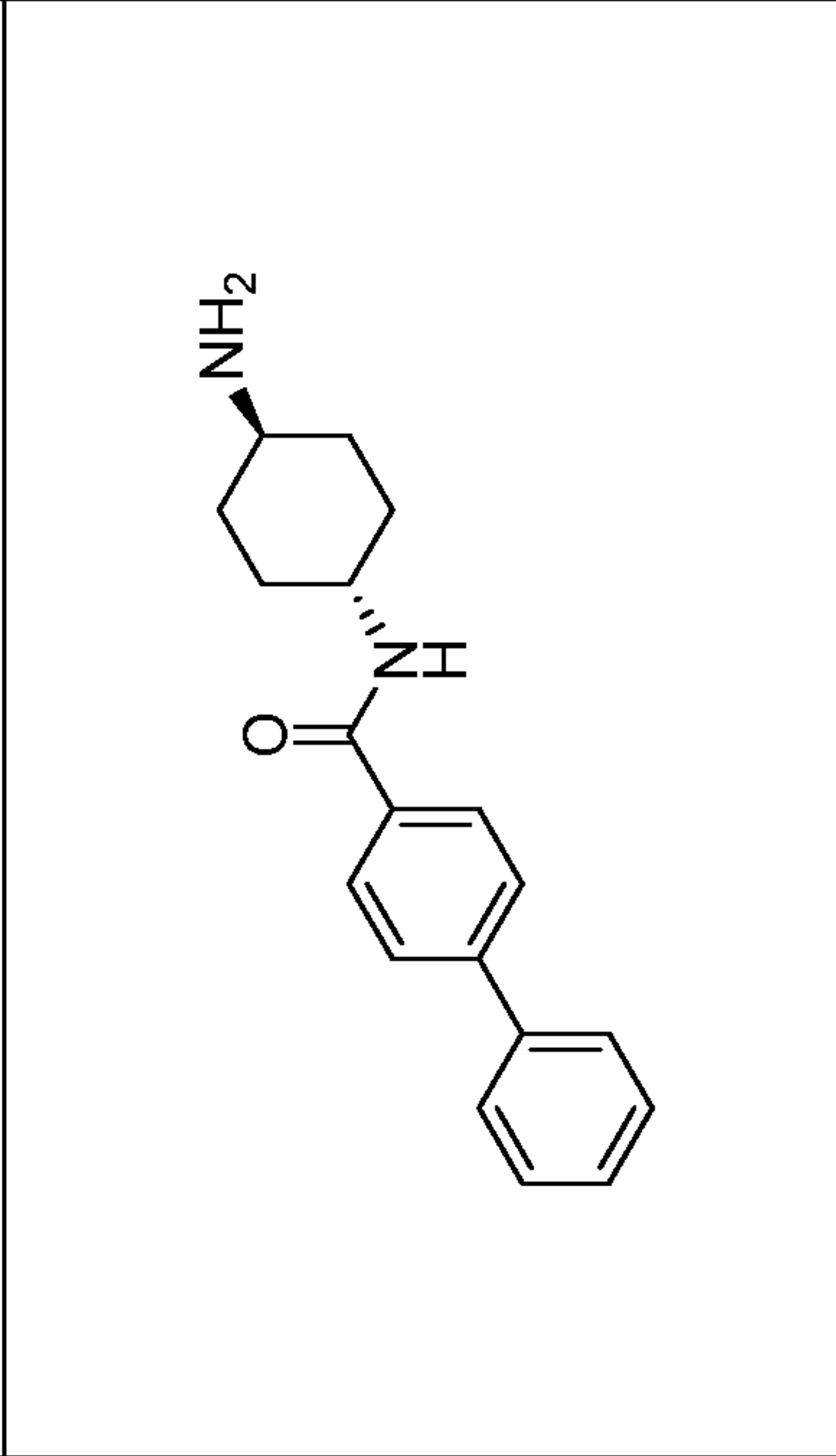
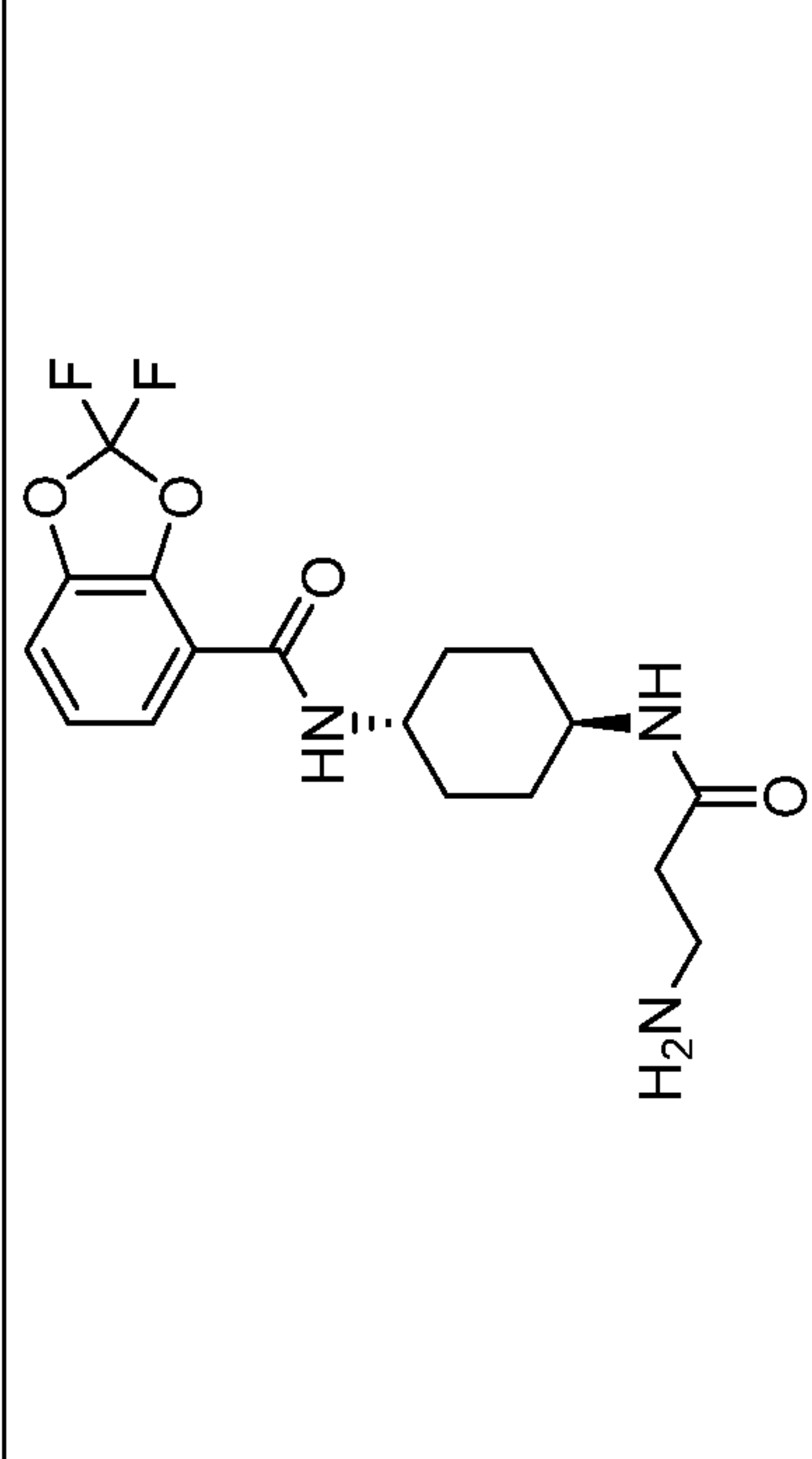
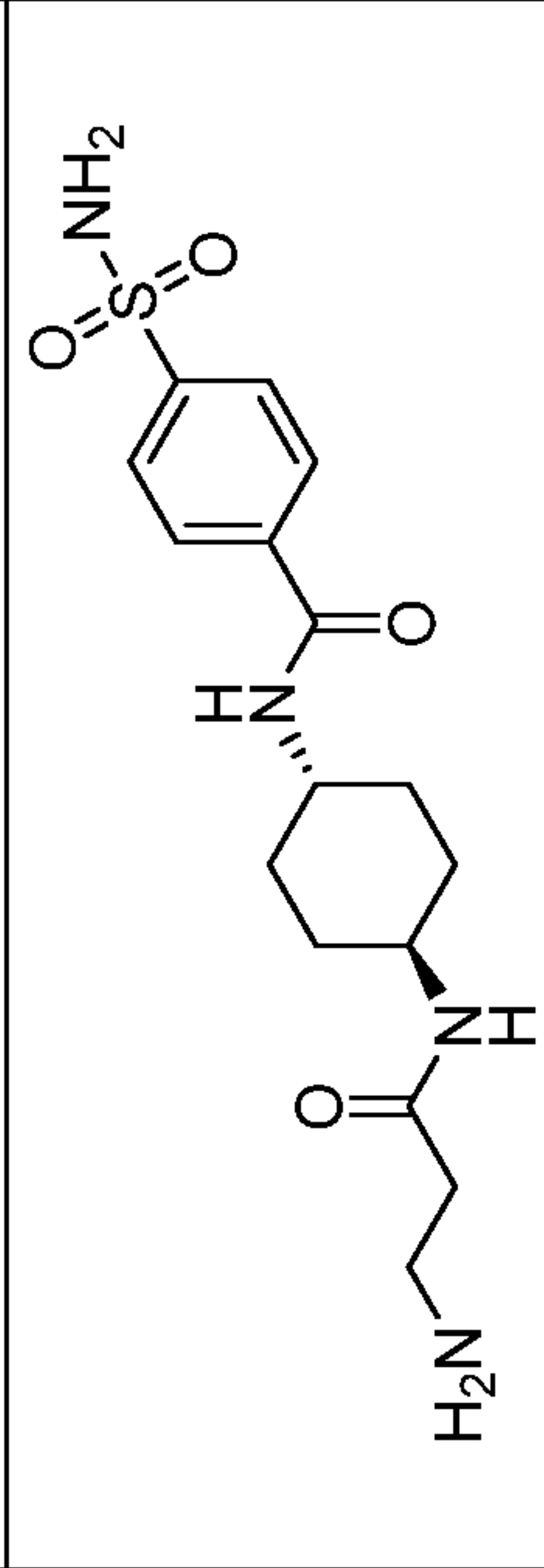
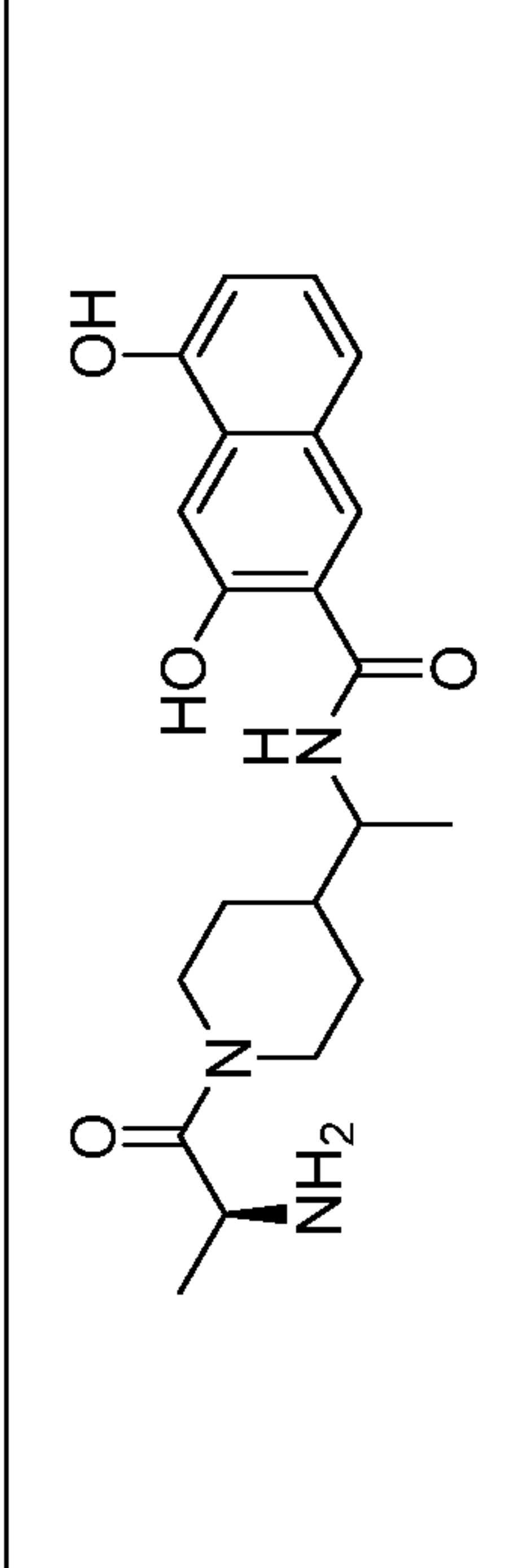
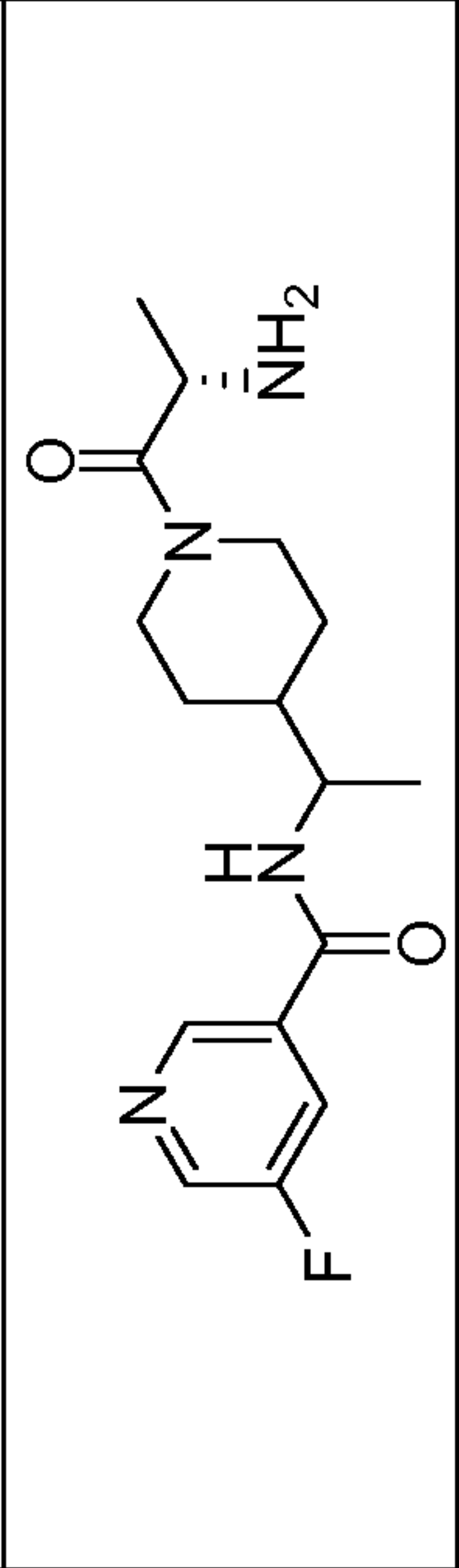
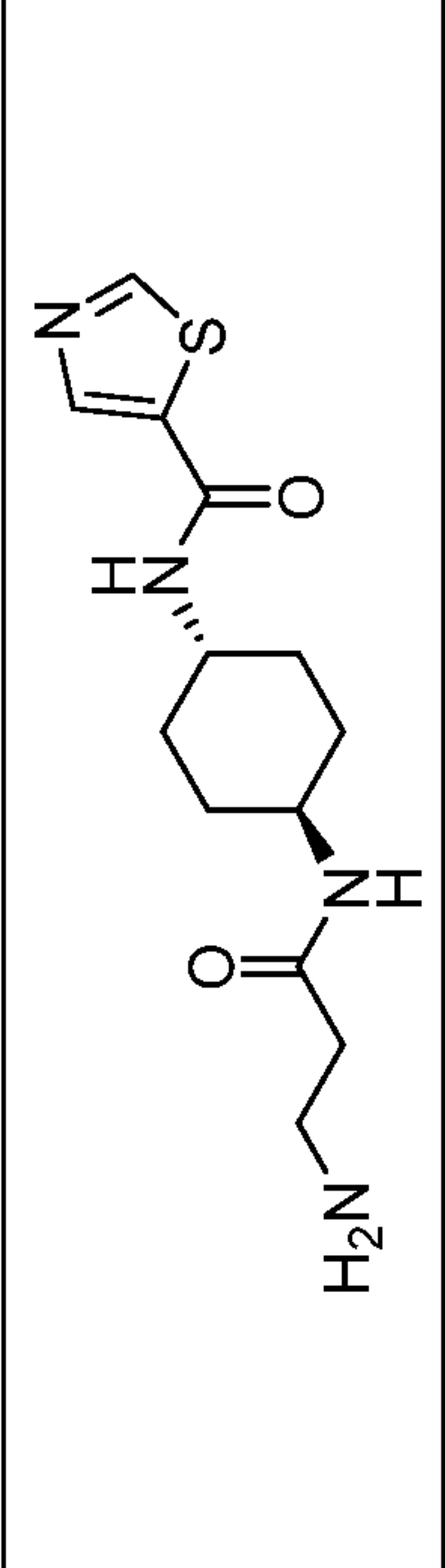
130		TFA	415		TFA
131		HCO OH	416		TFA
132		TFA	417		TFA
133		TFA	418		TFA
134		TFA	419		TFA

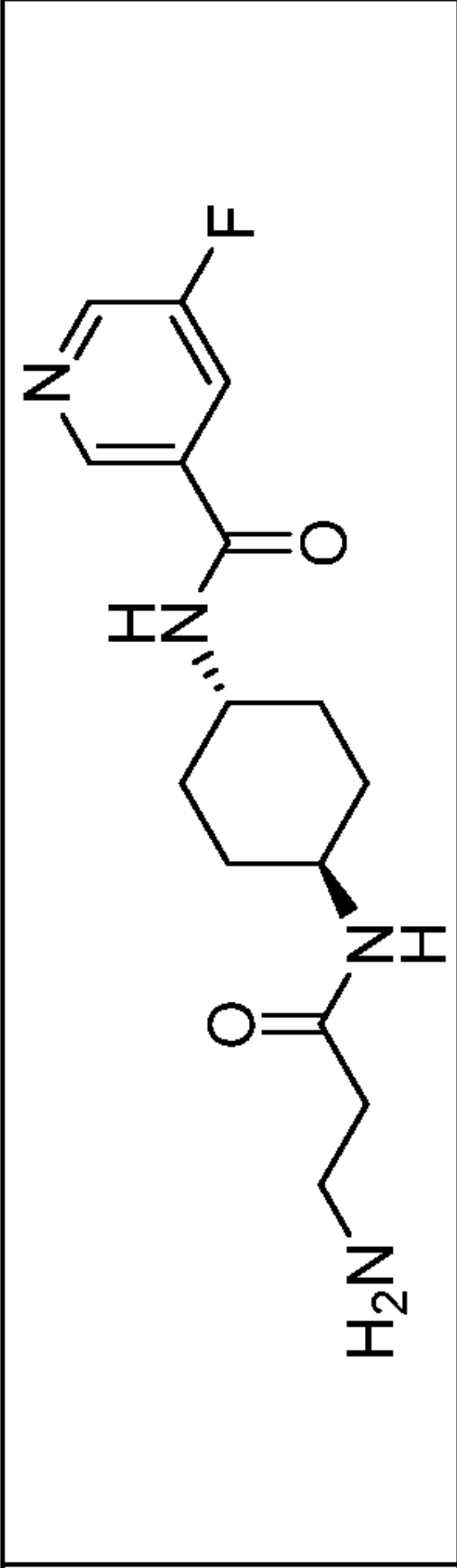
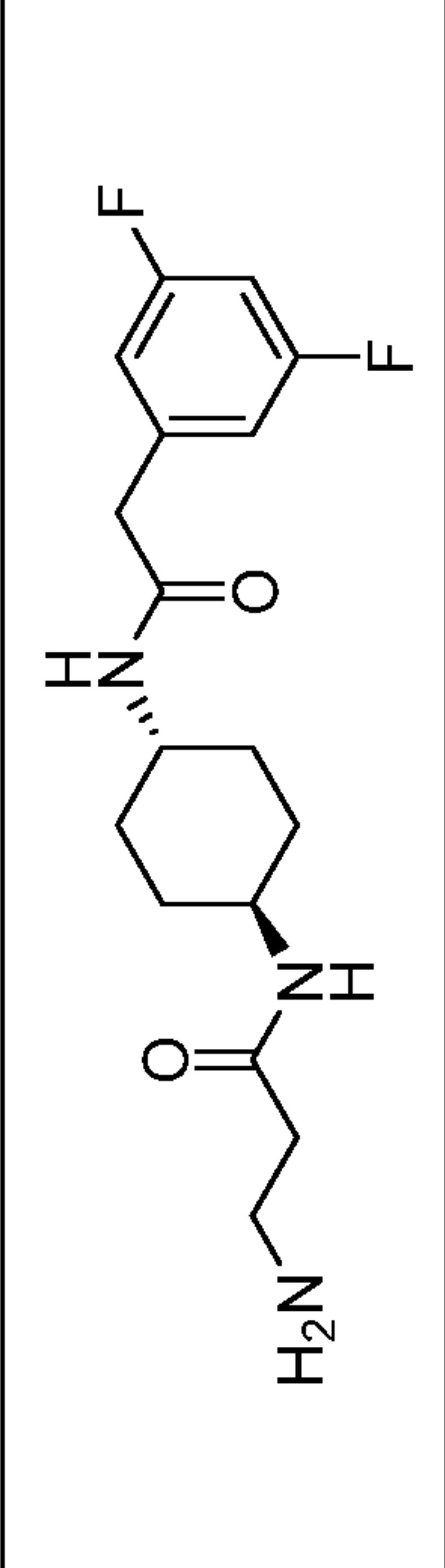
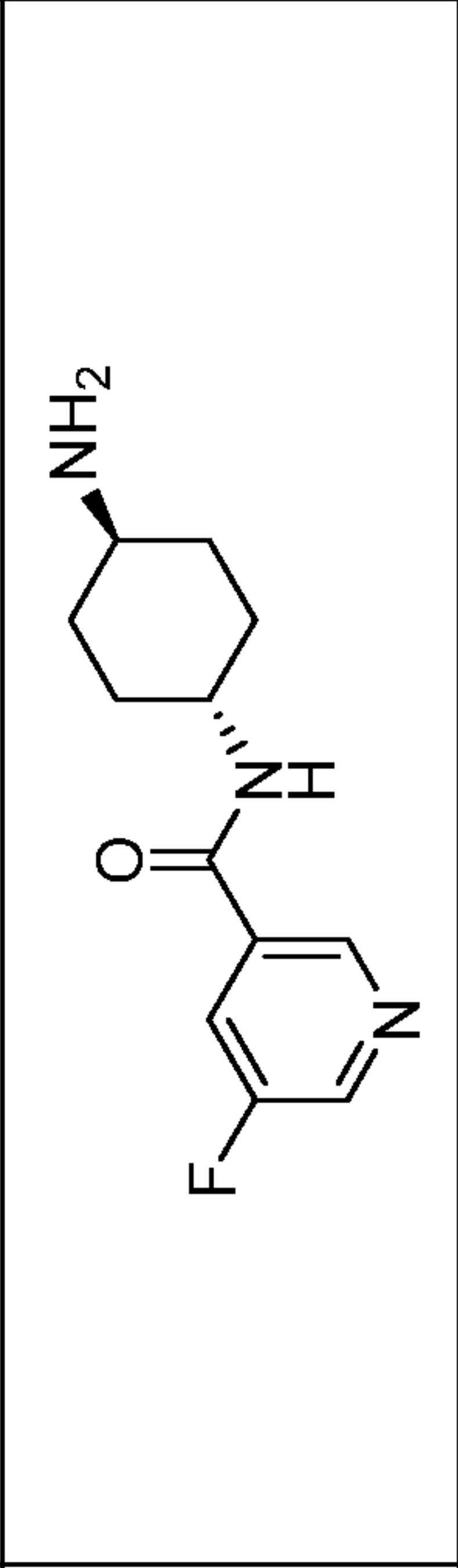
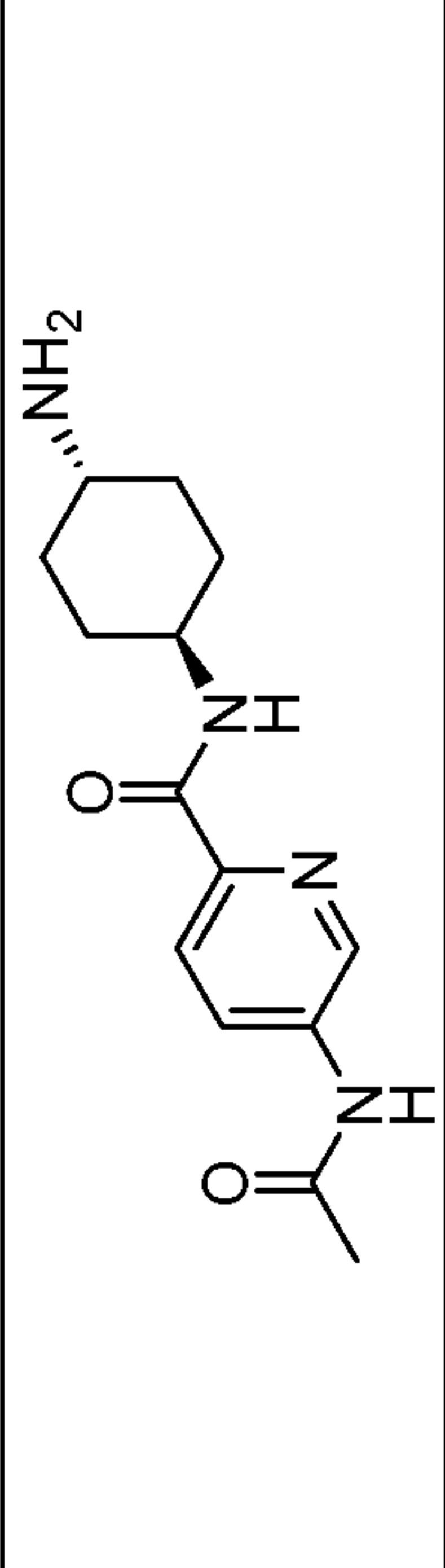
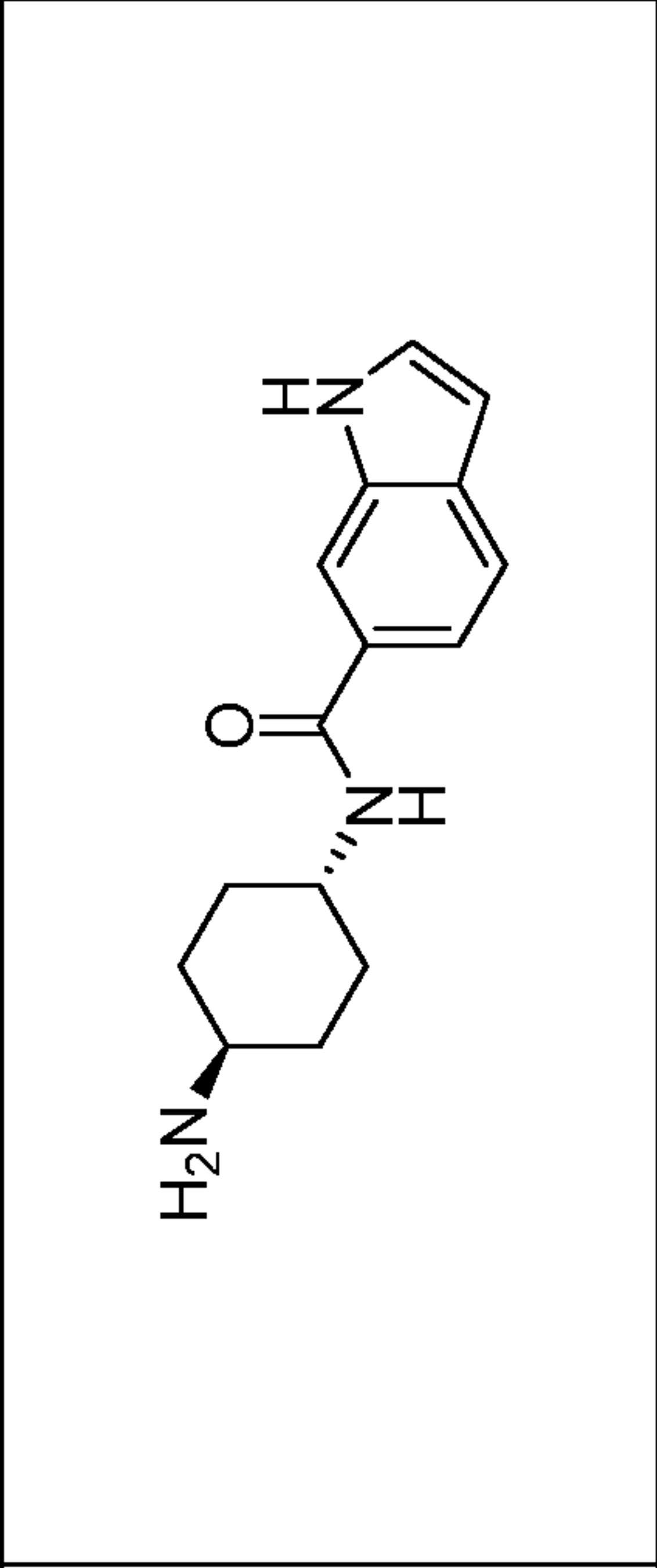
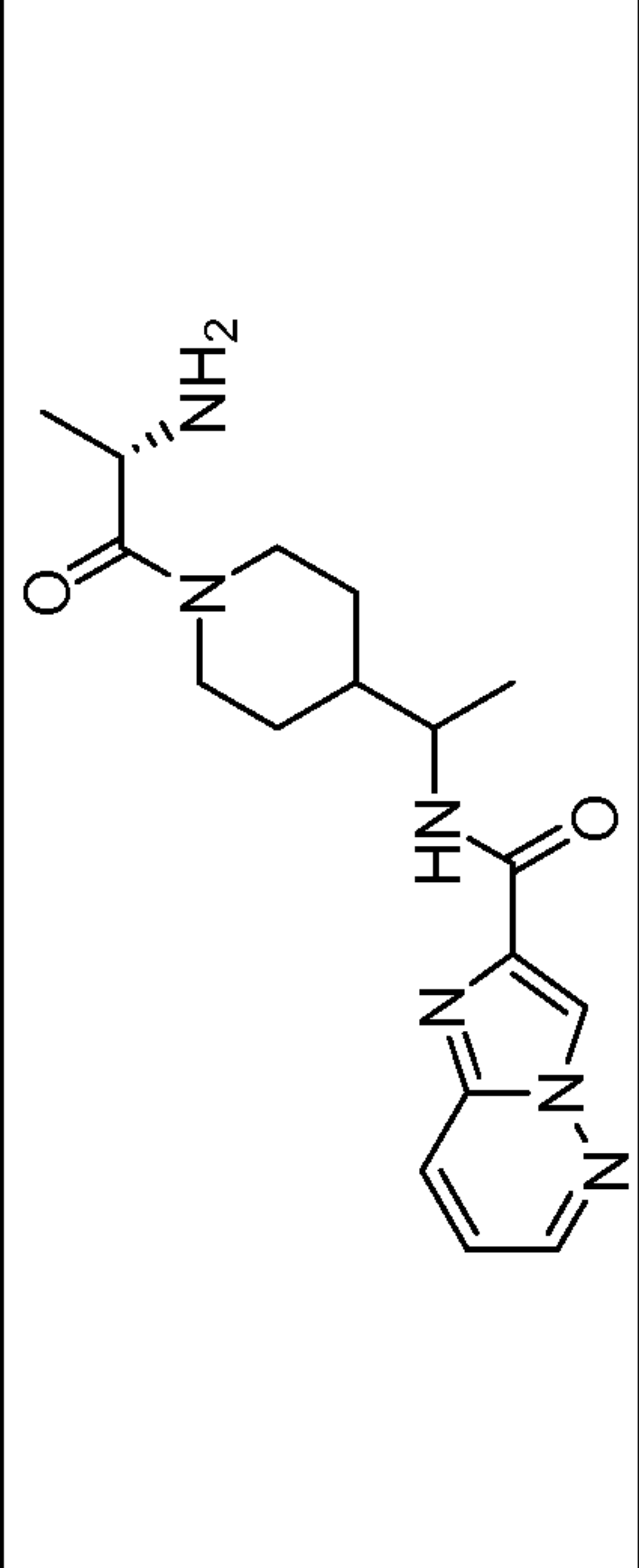
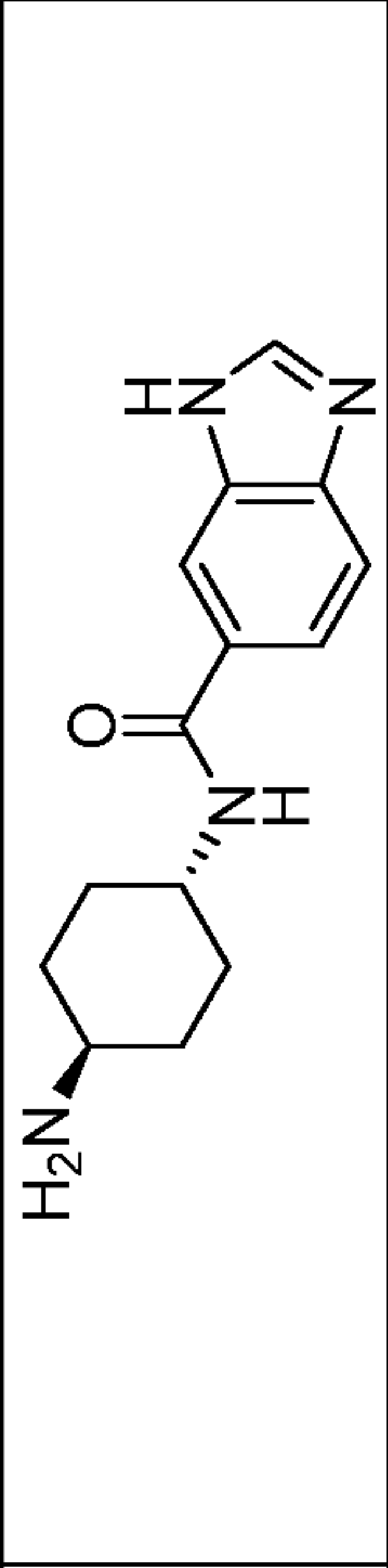
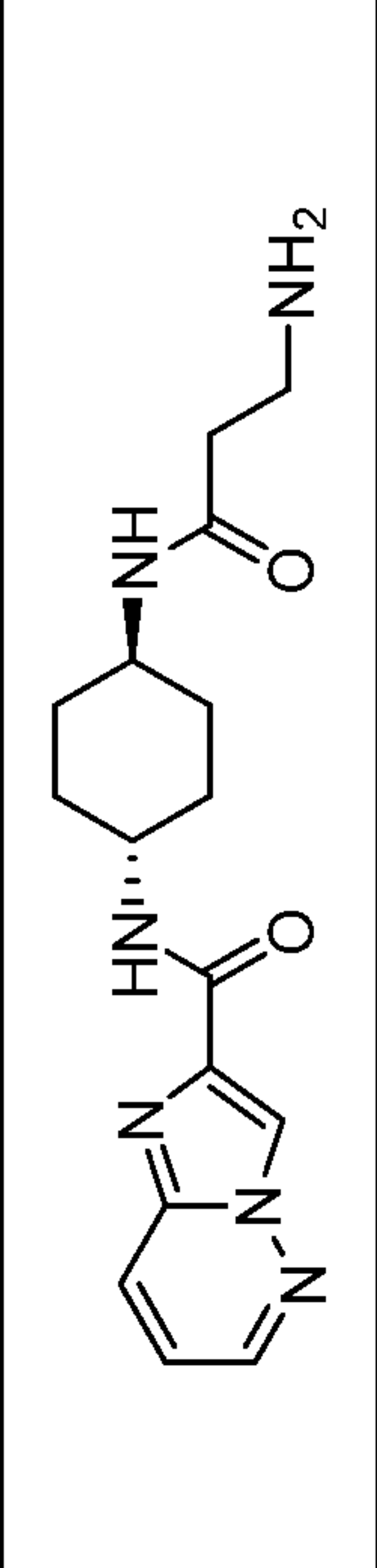
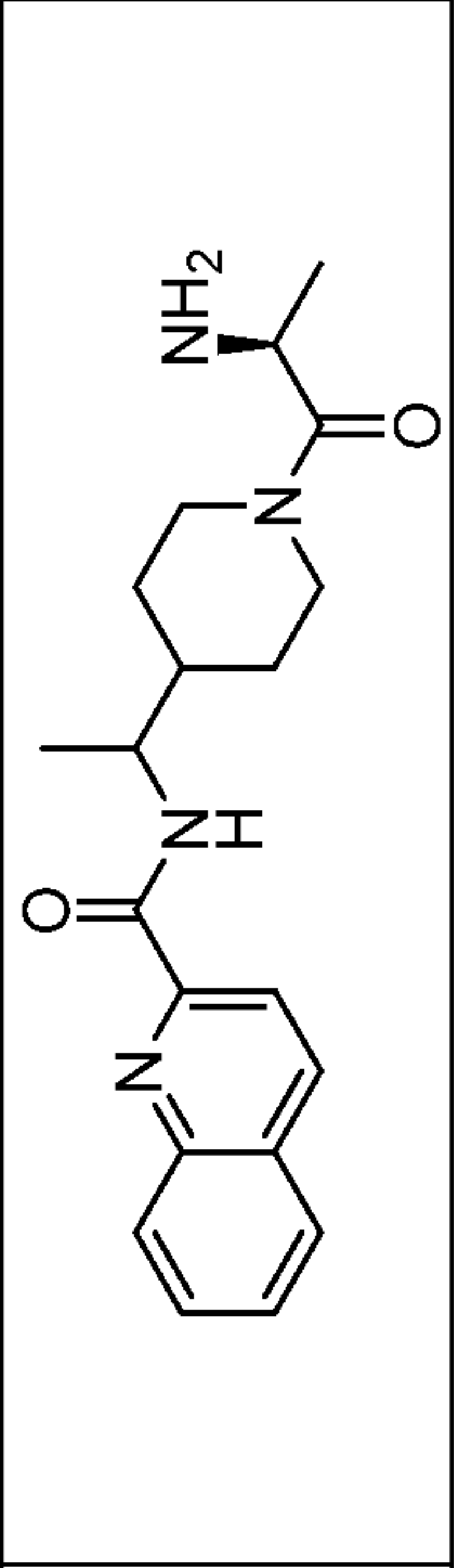
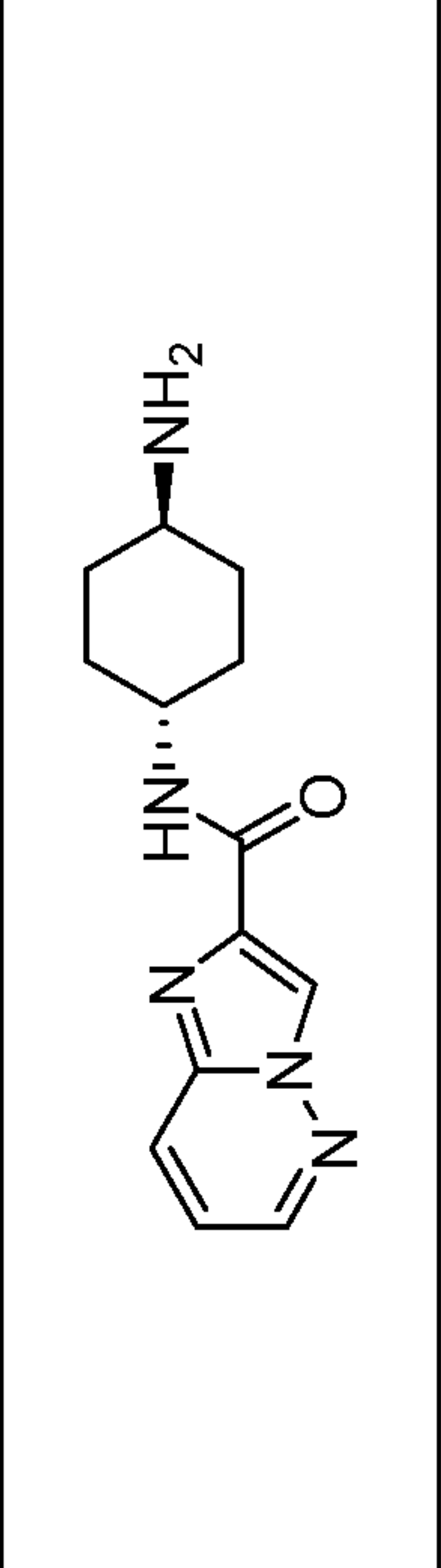
135		TFA	420		TFA
136		HCl	421		TFA
137		HCl	422		TFA
138		HCl	423		TFA
139		HCl	424		TFA

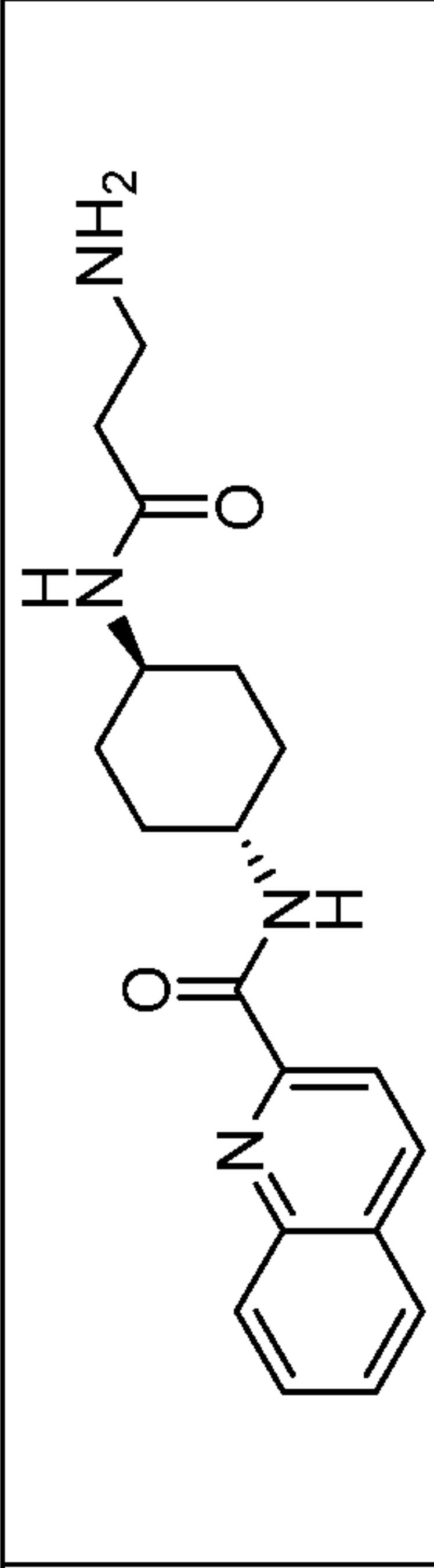
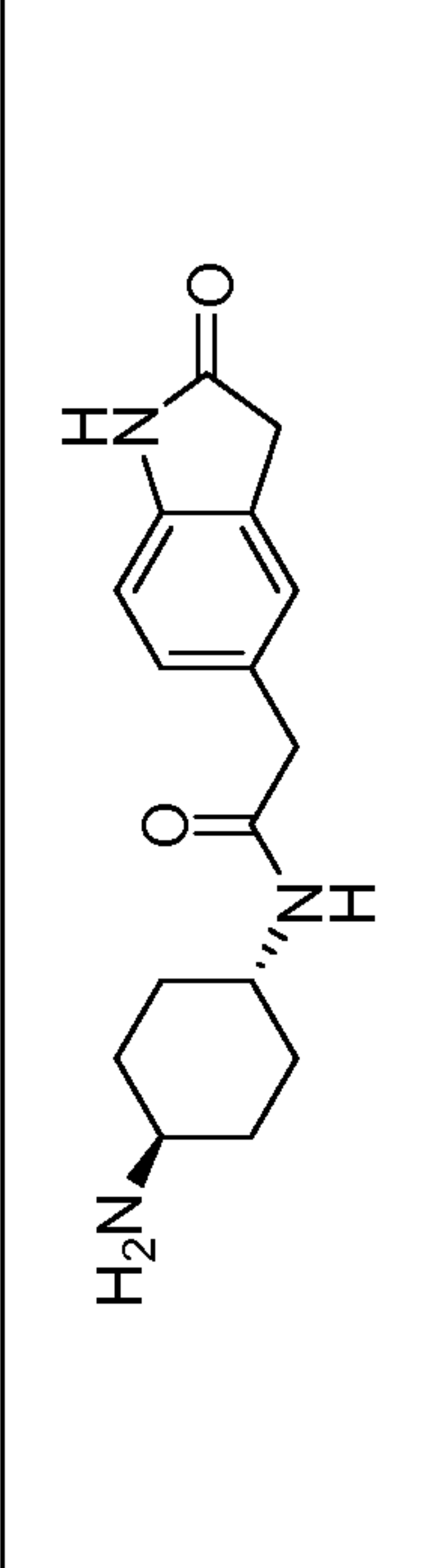
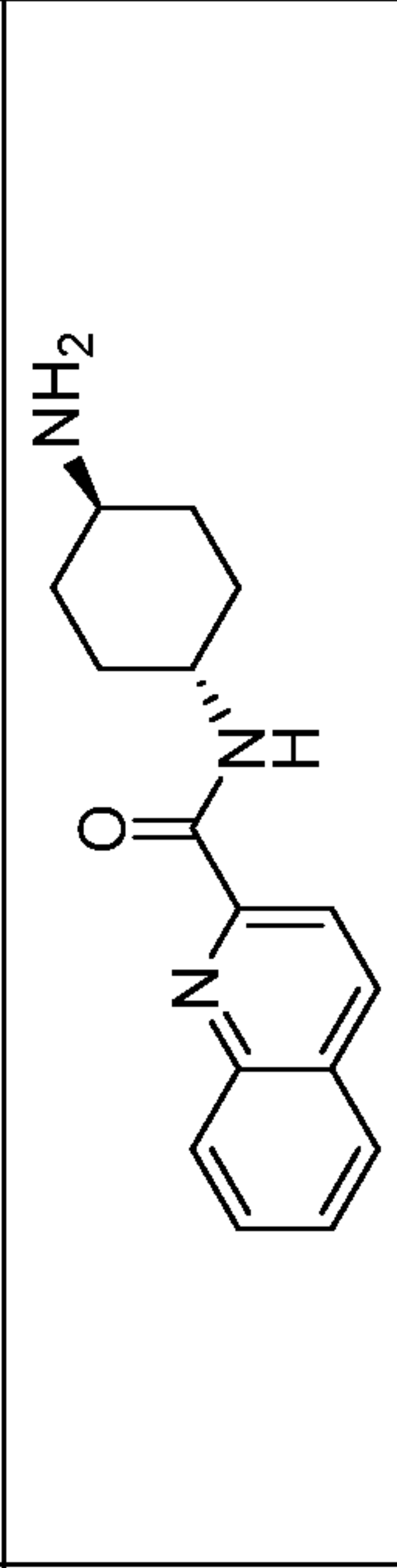
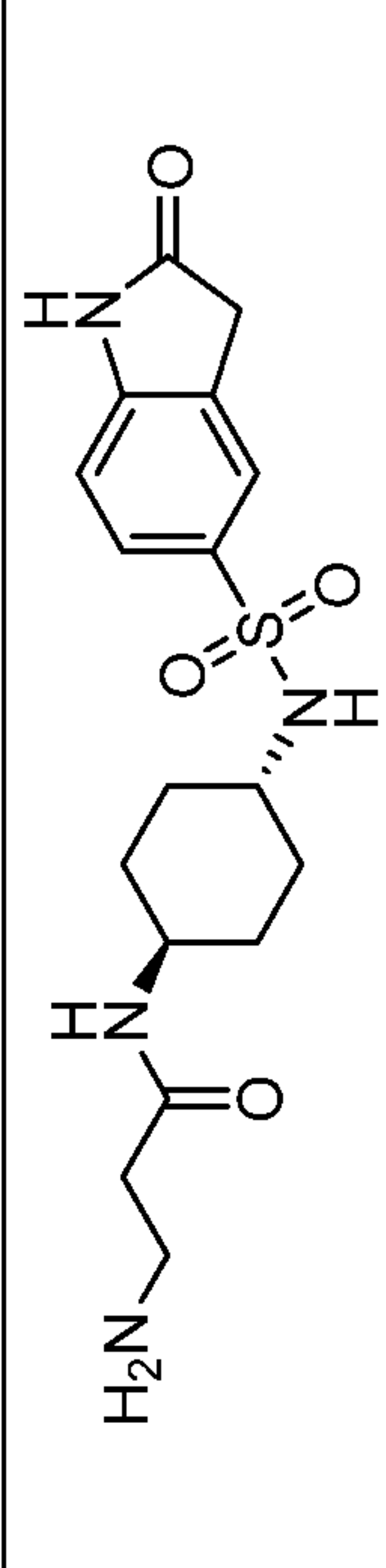
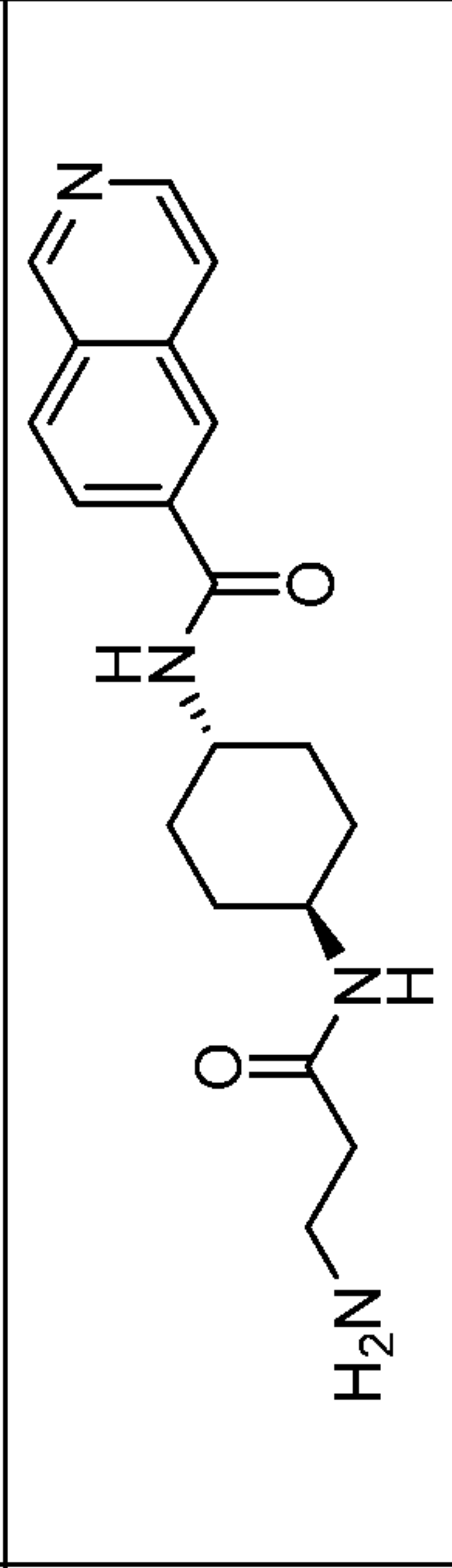
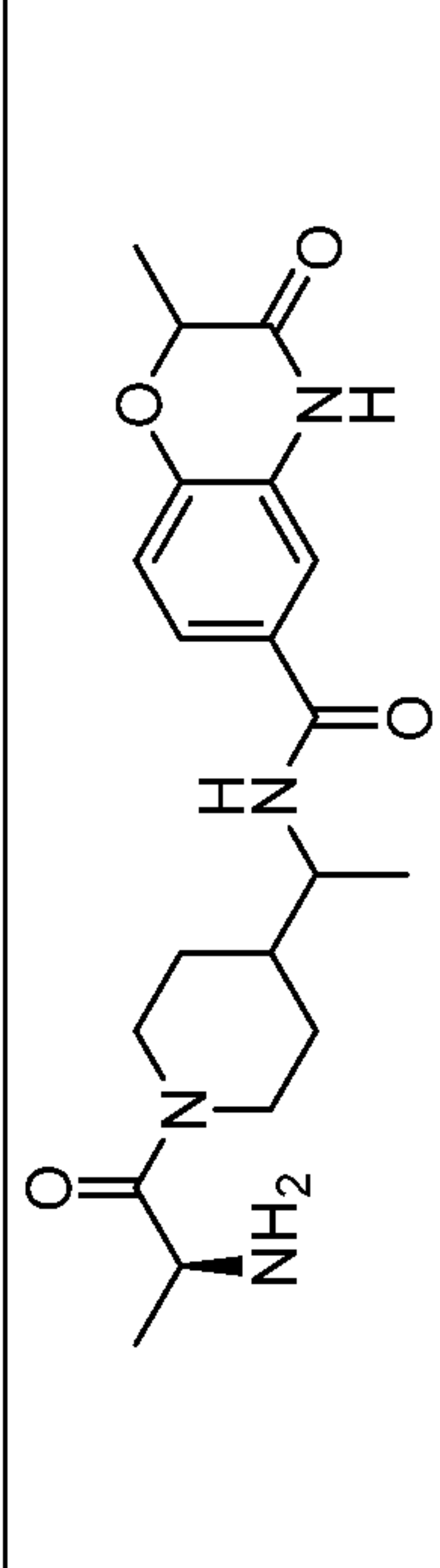
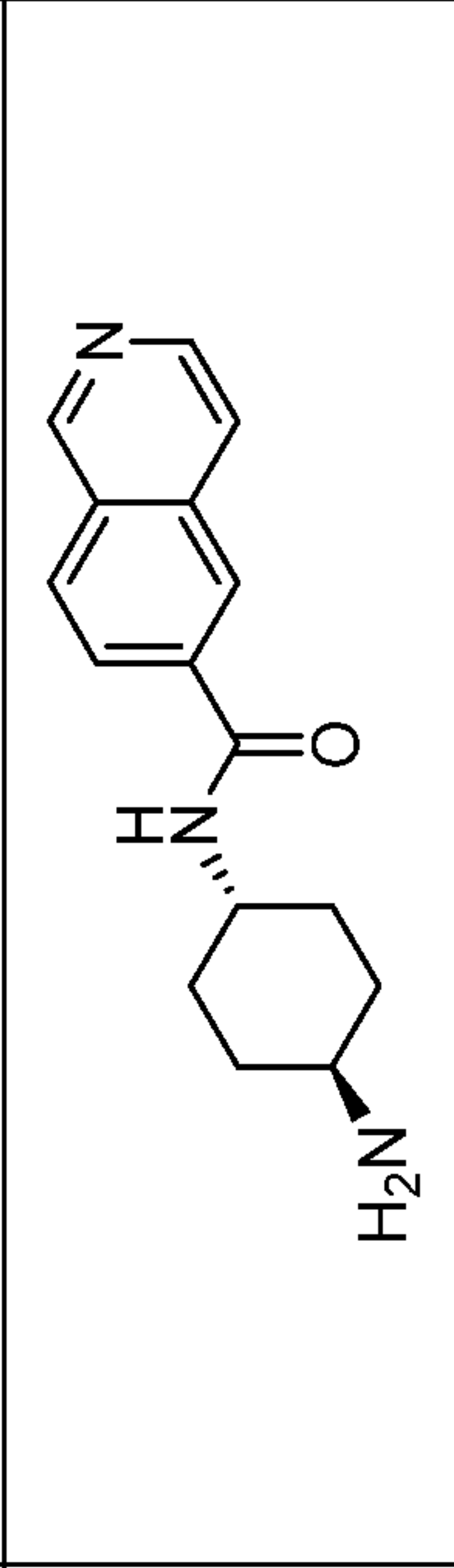
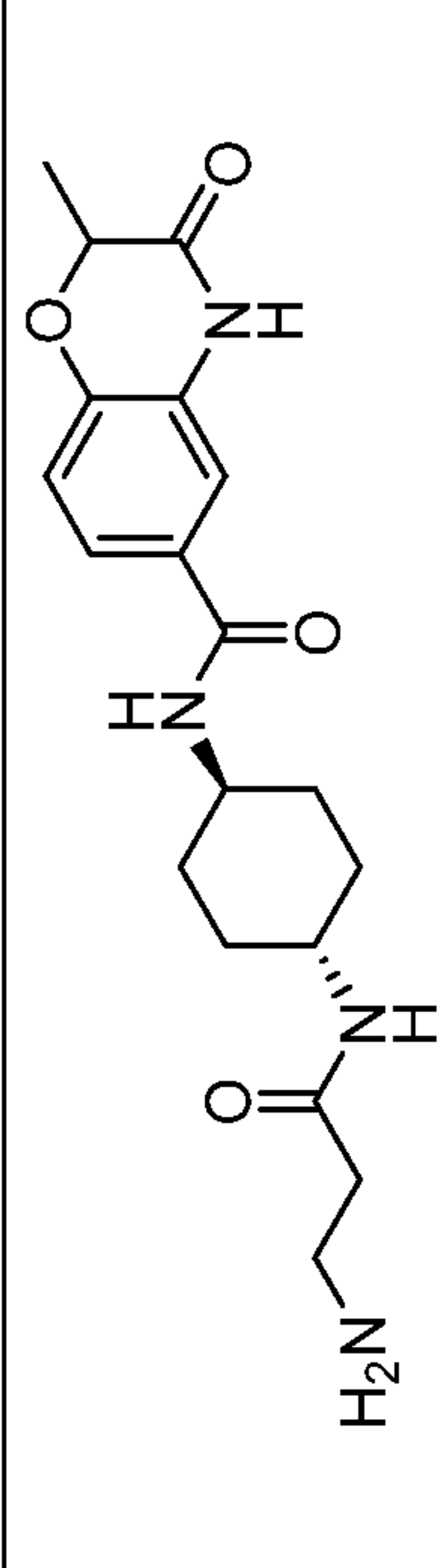
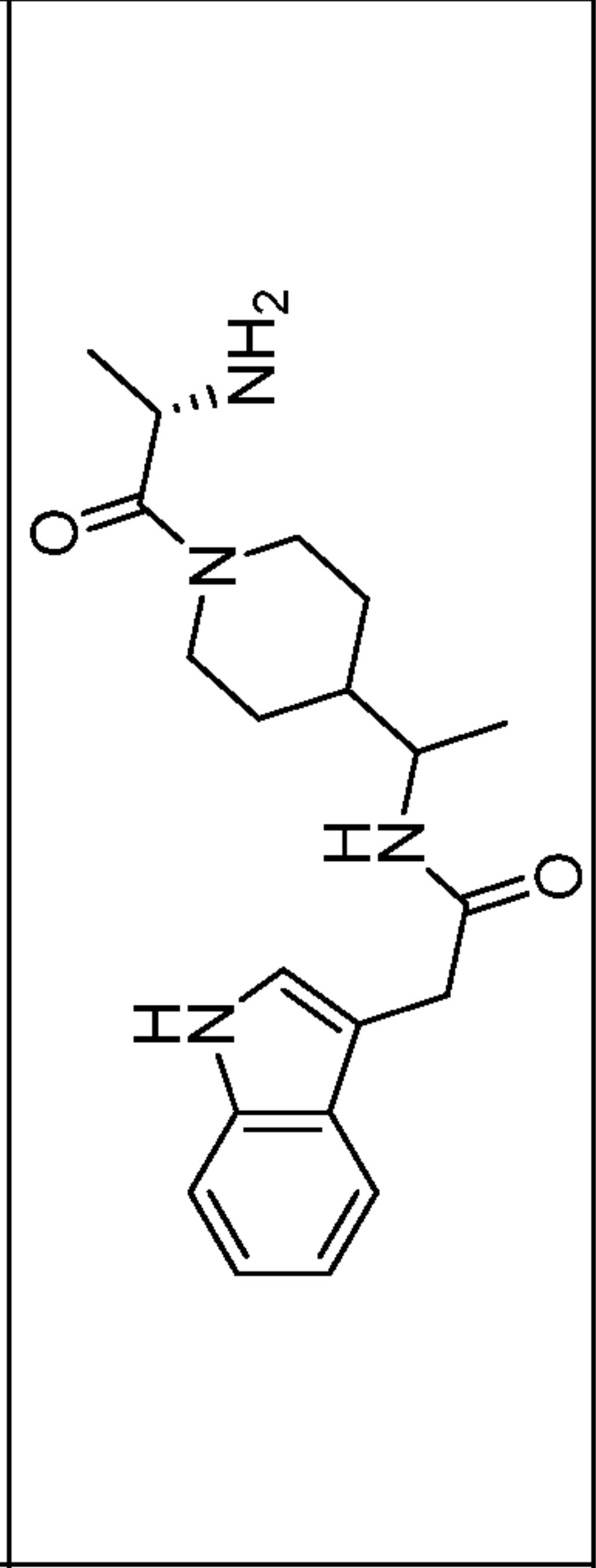
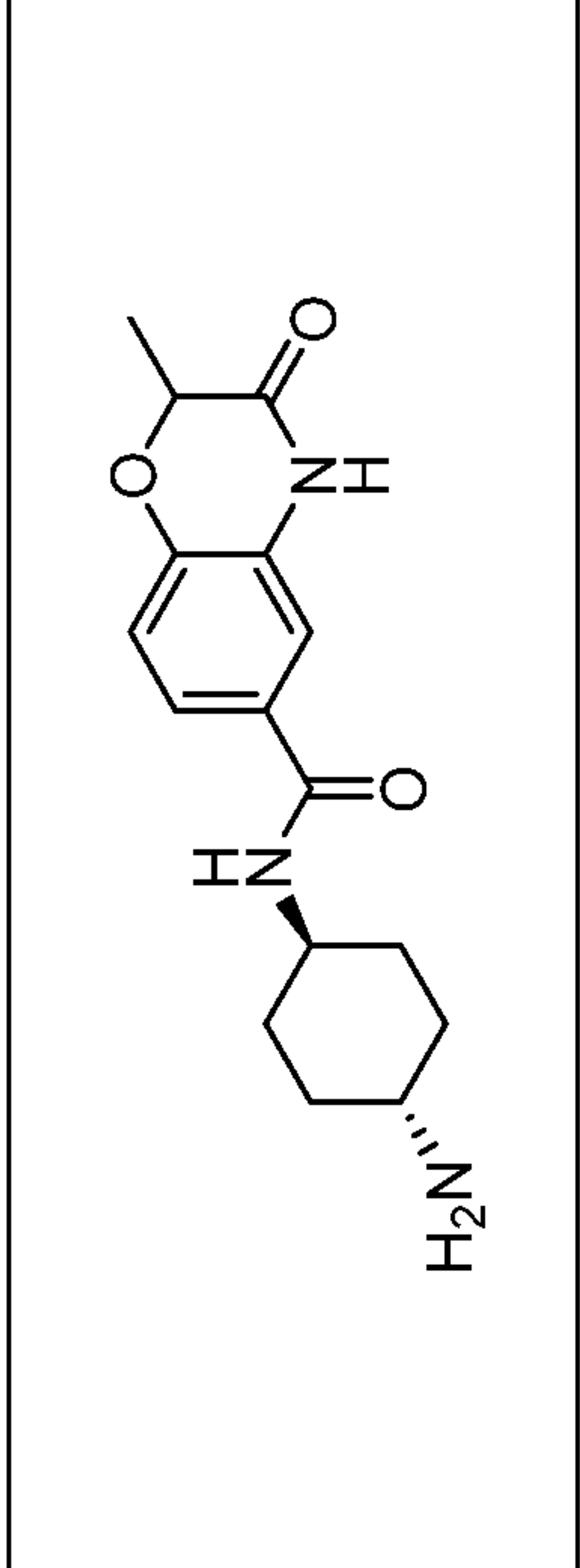
140		HCl	425		TFA
141		HCl	426		TFA
142		HCl	427		TFA
143		HCl	428		TFA
144		HCl	429		TFA

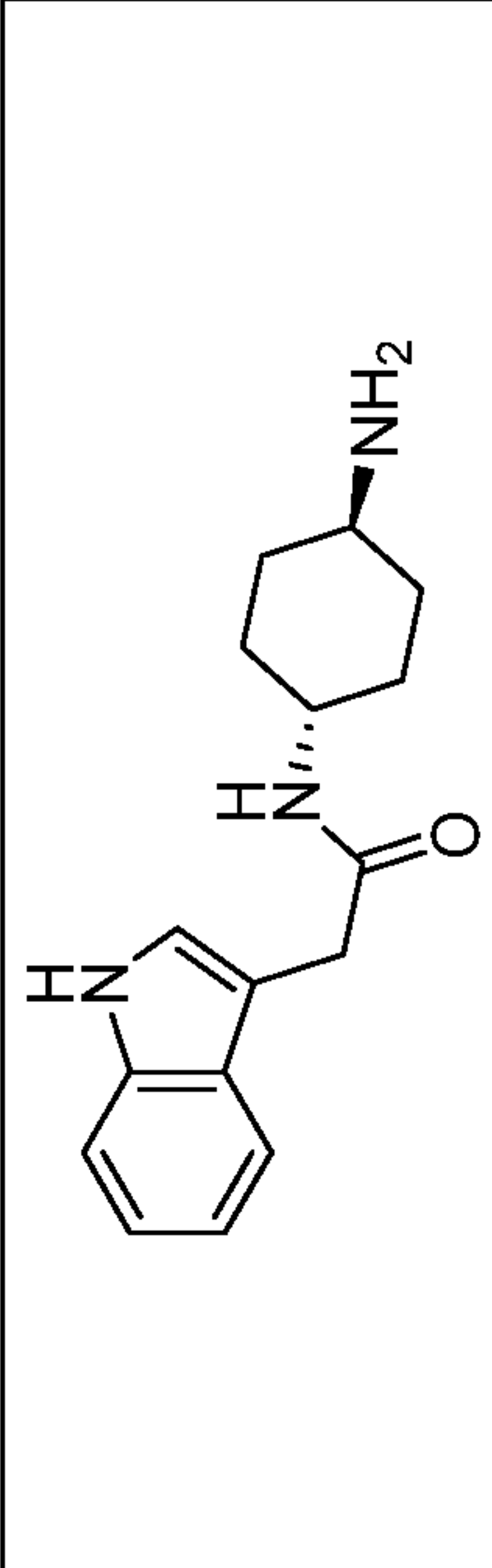
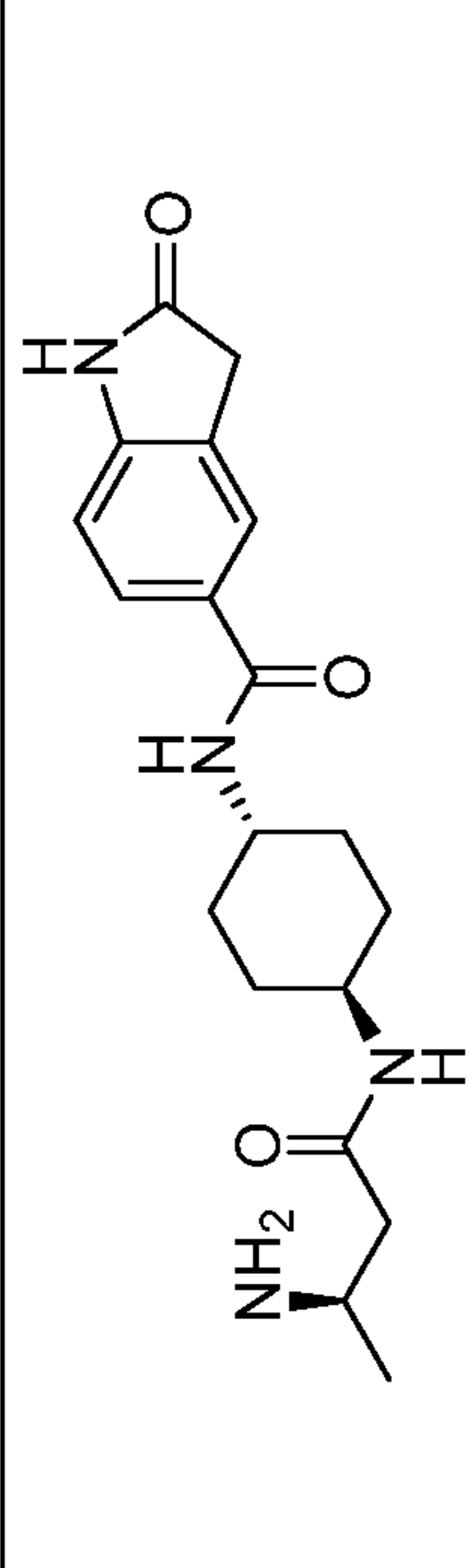
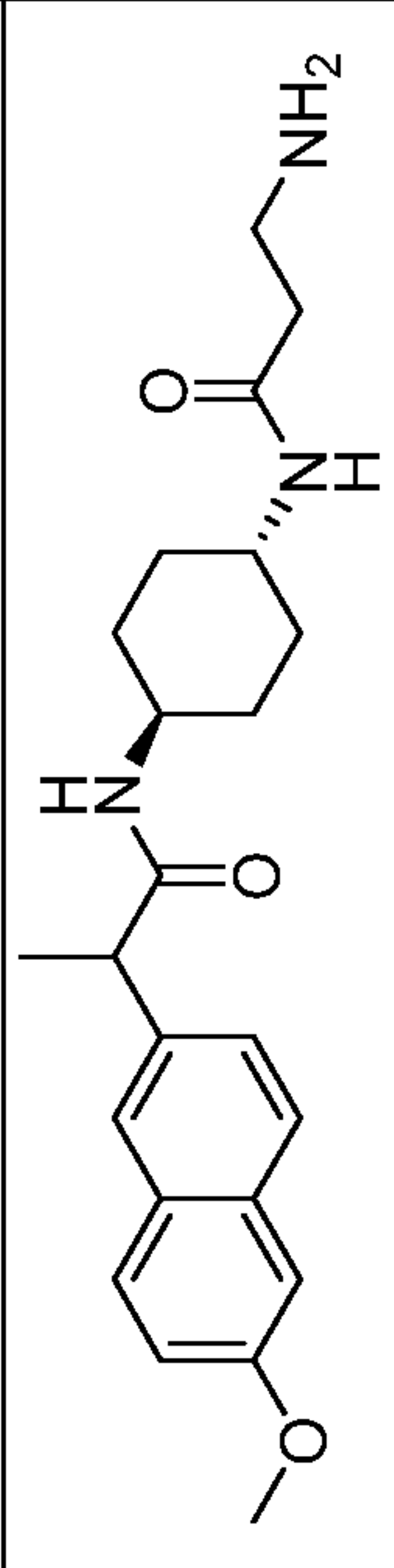
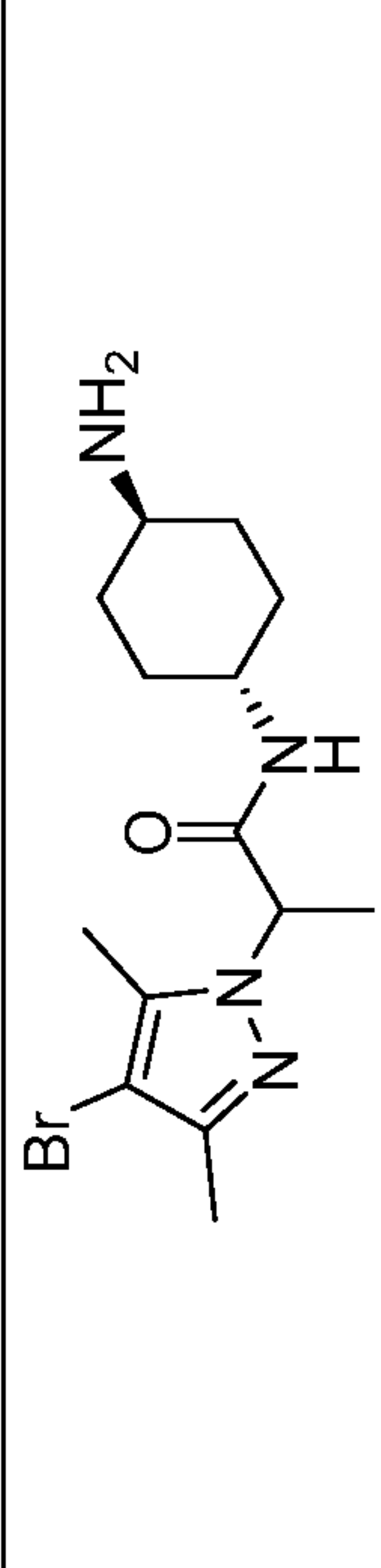
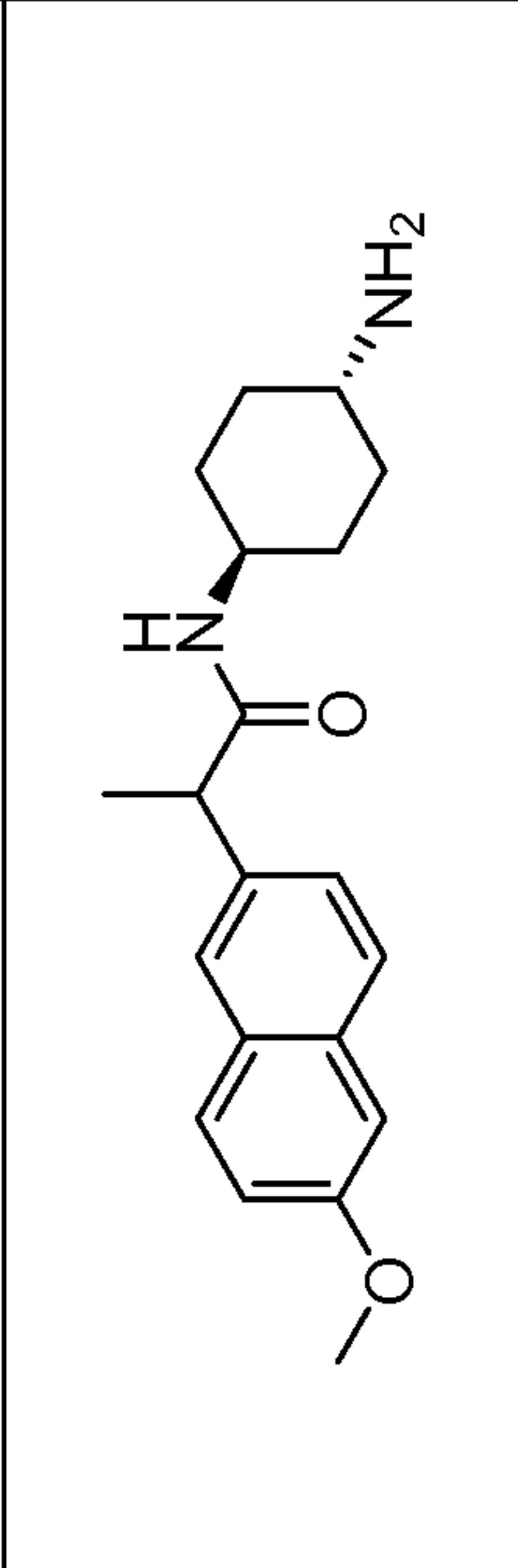
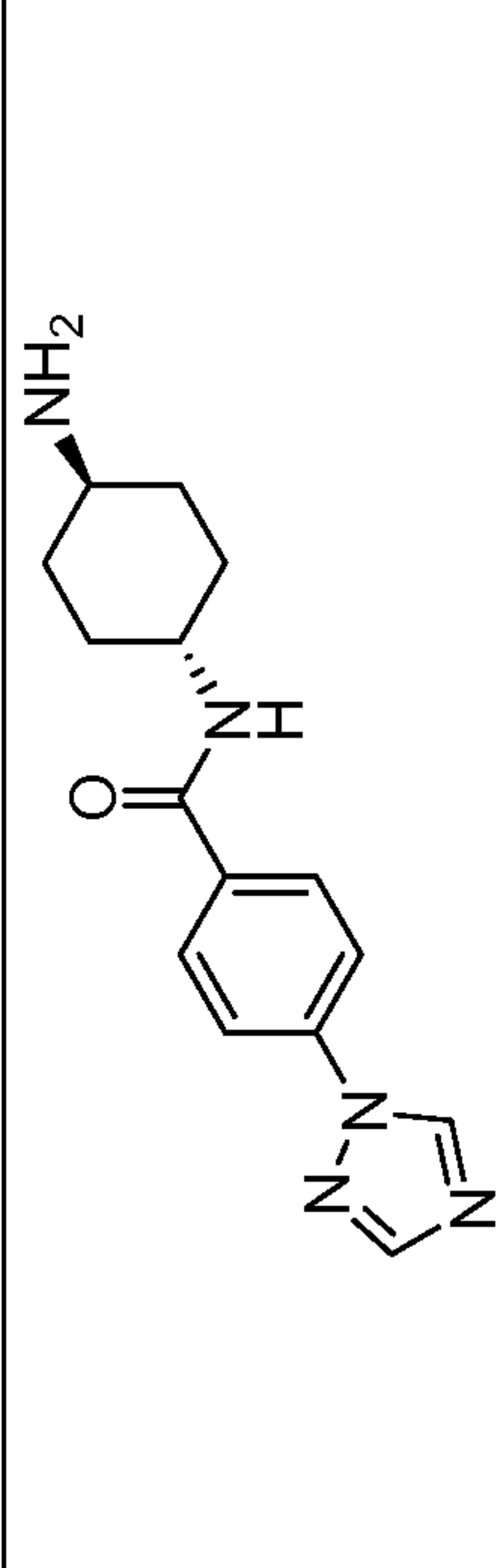
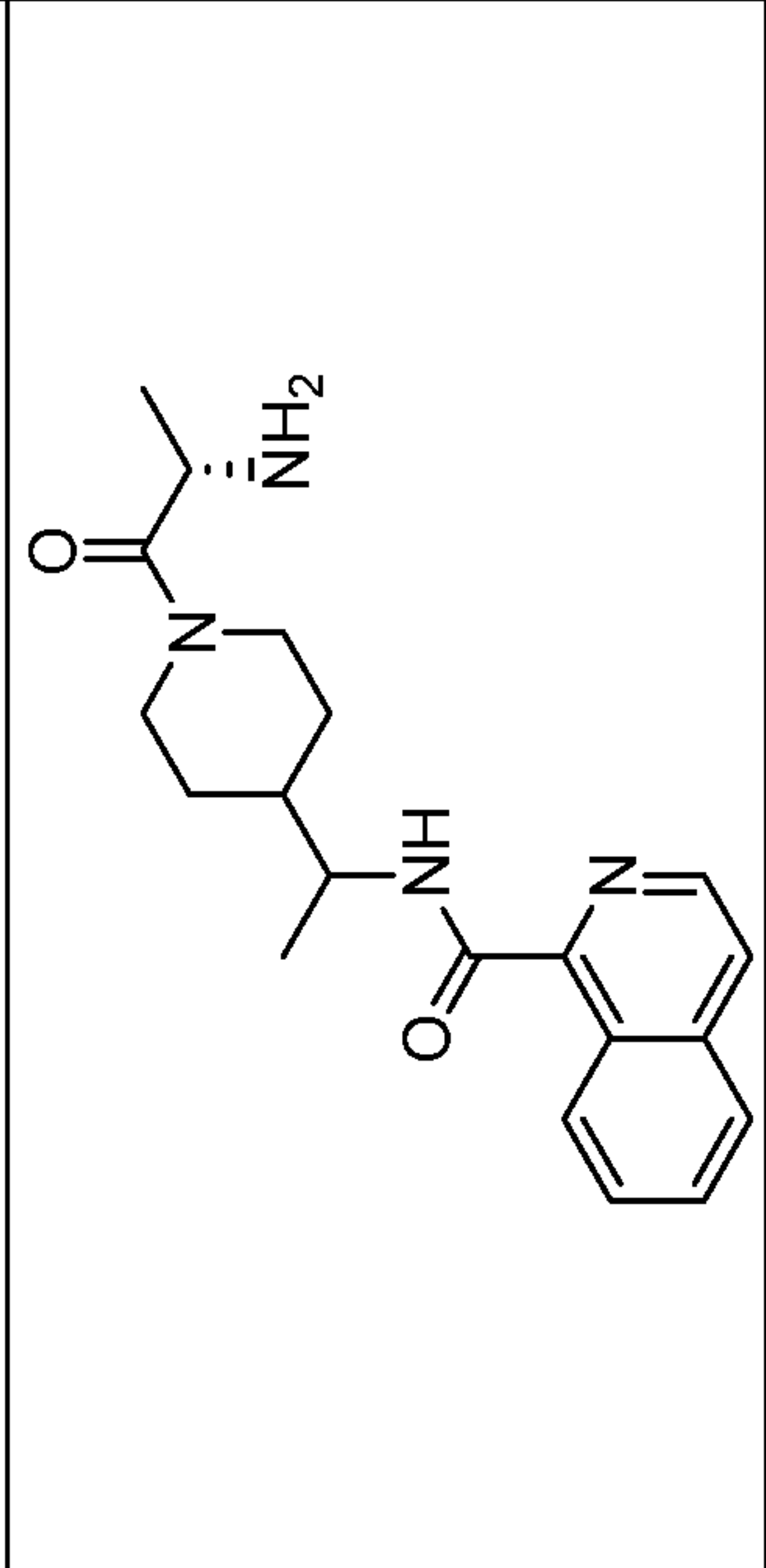
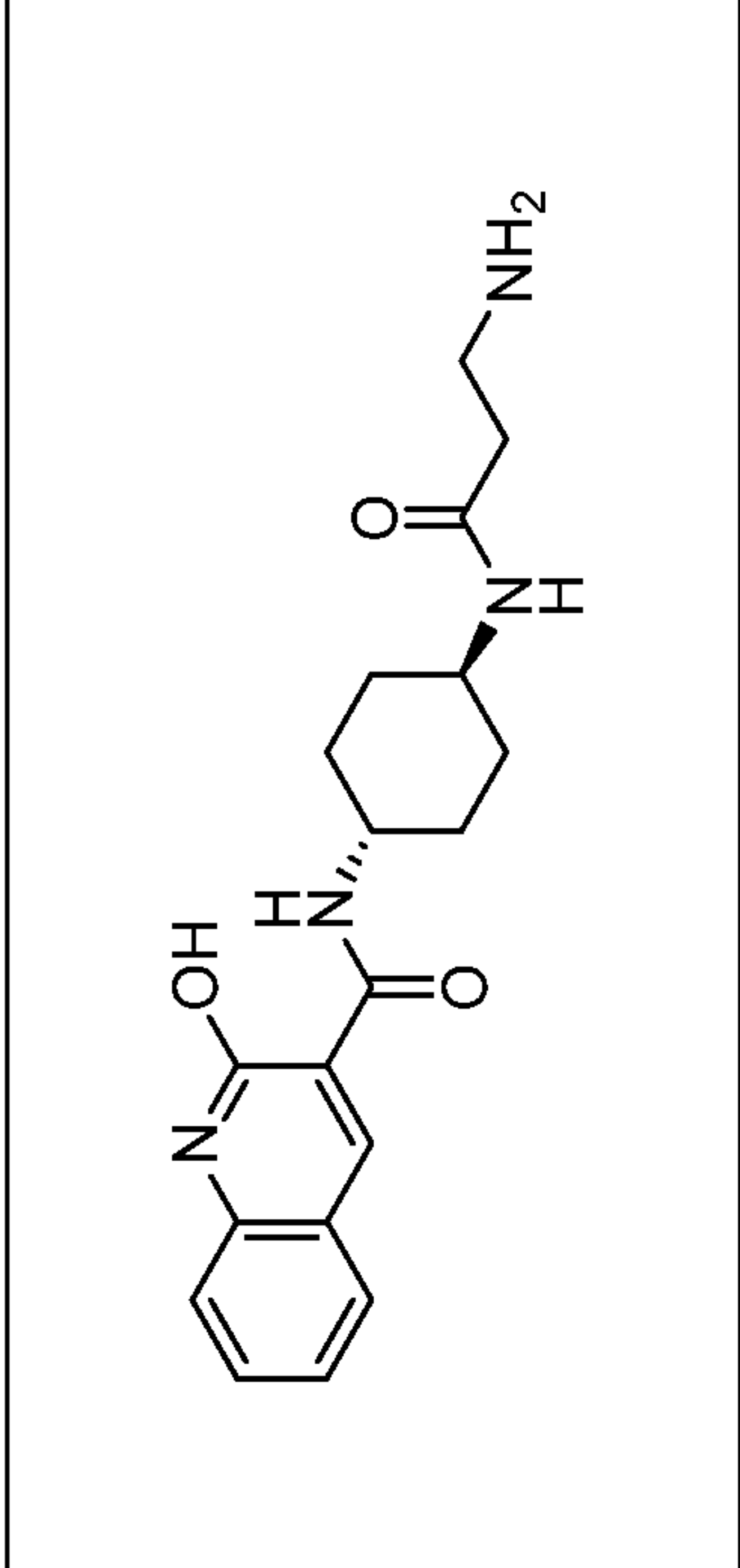
145		HCl	430		HCl
146		HCl	431		TFA
147		HCl	432		TFA
148		HCl	433		HCl

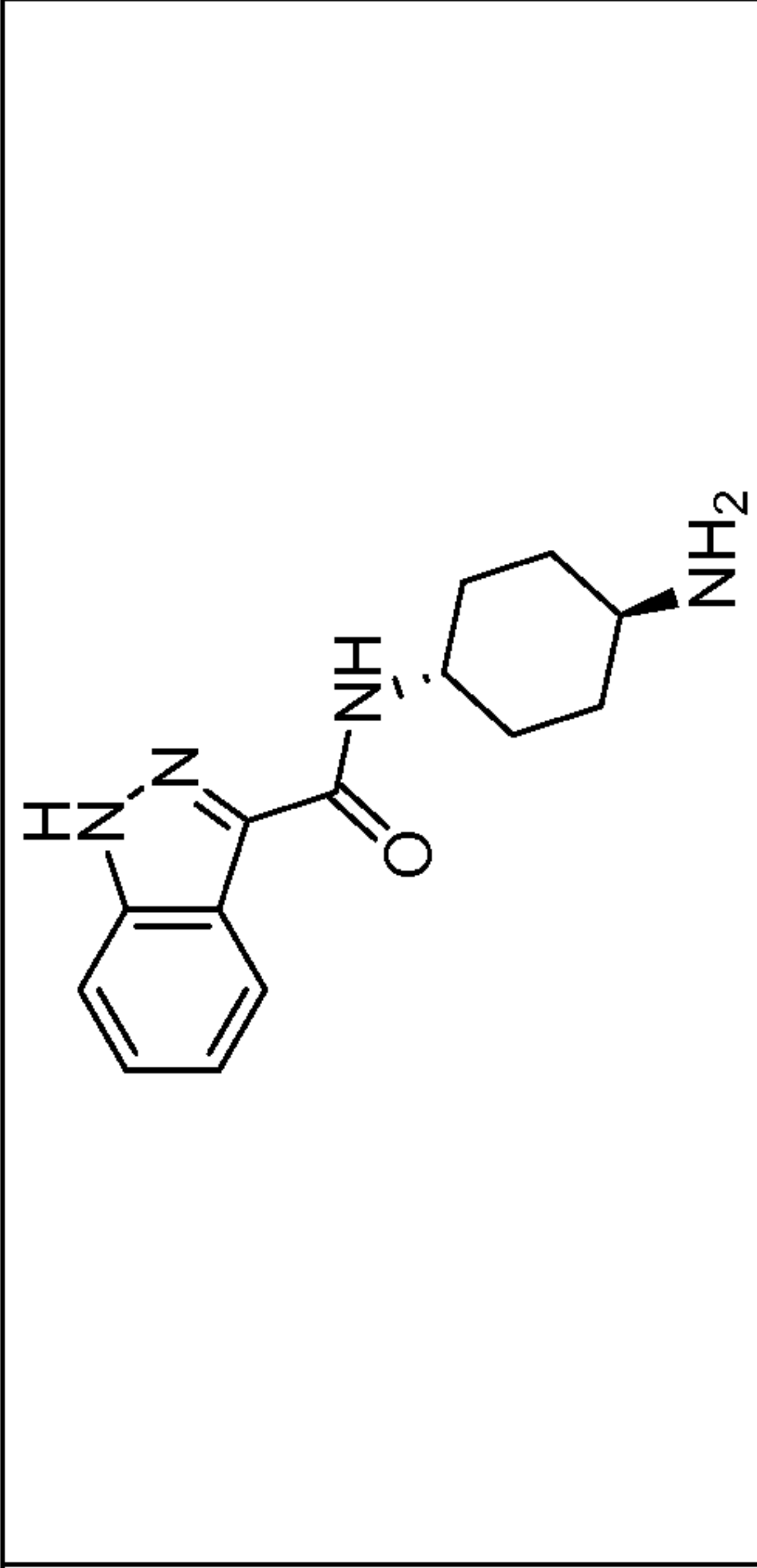
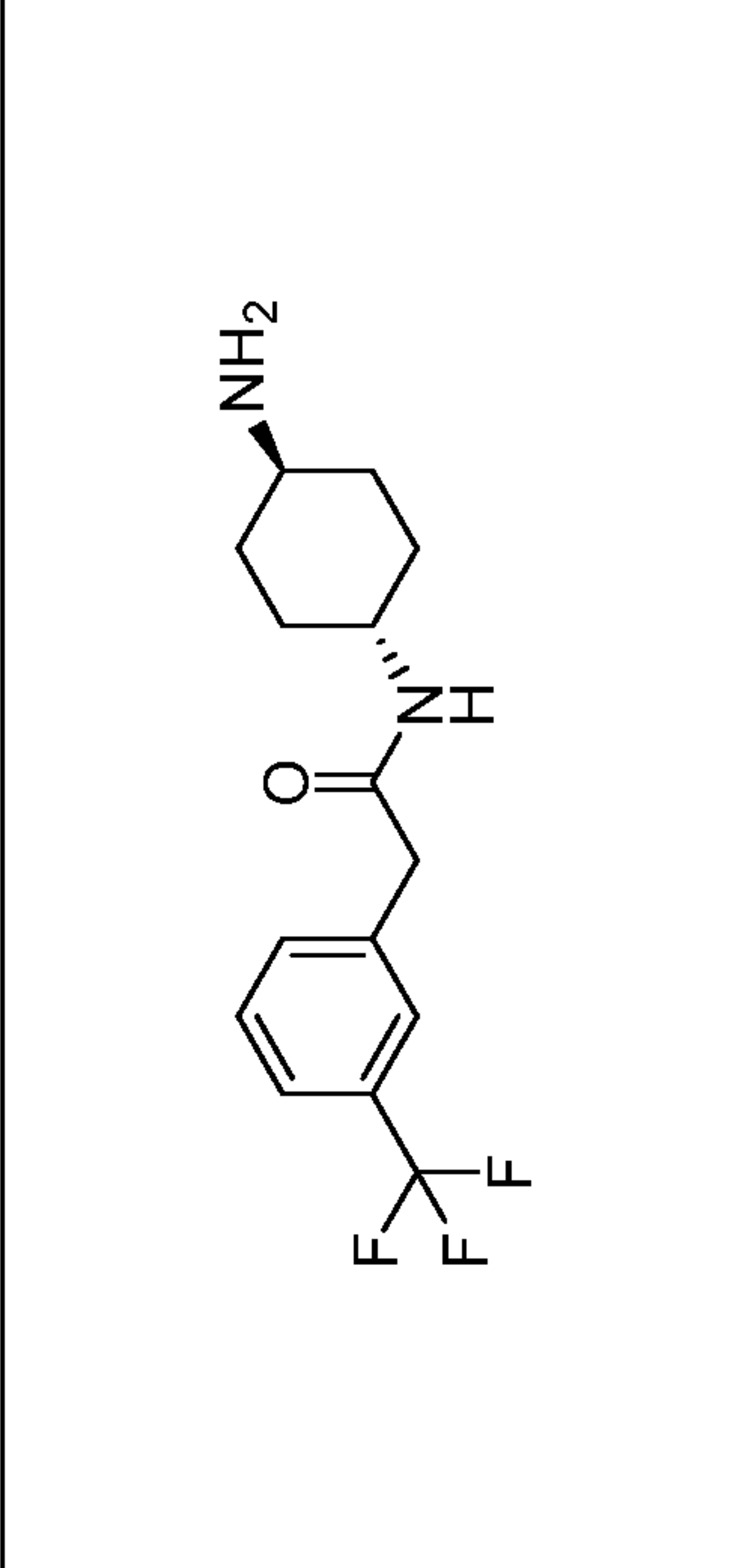
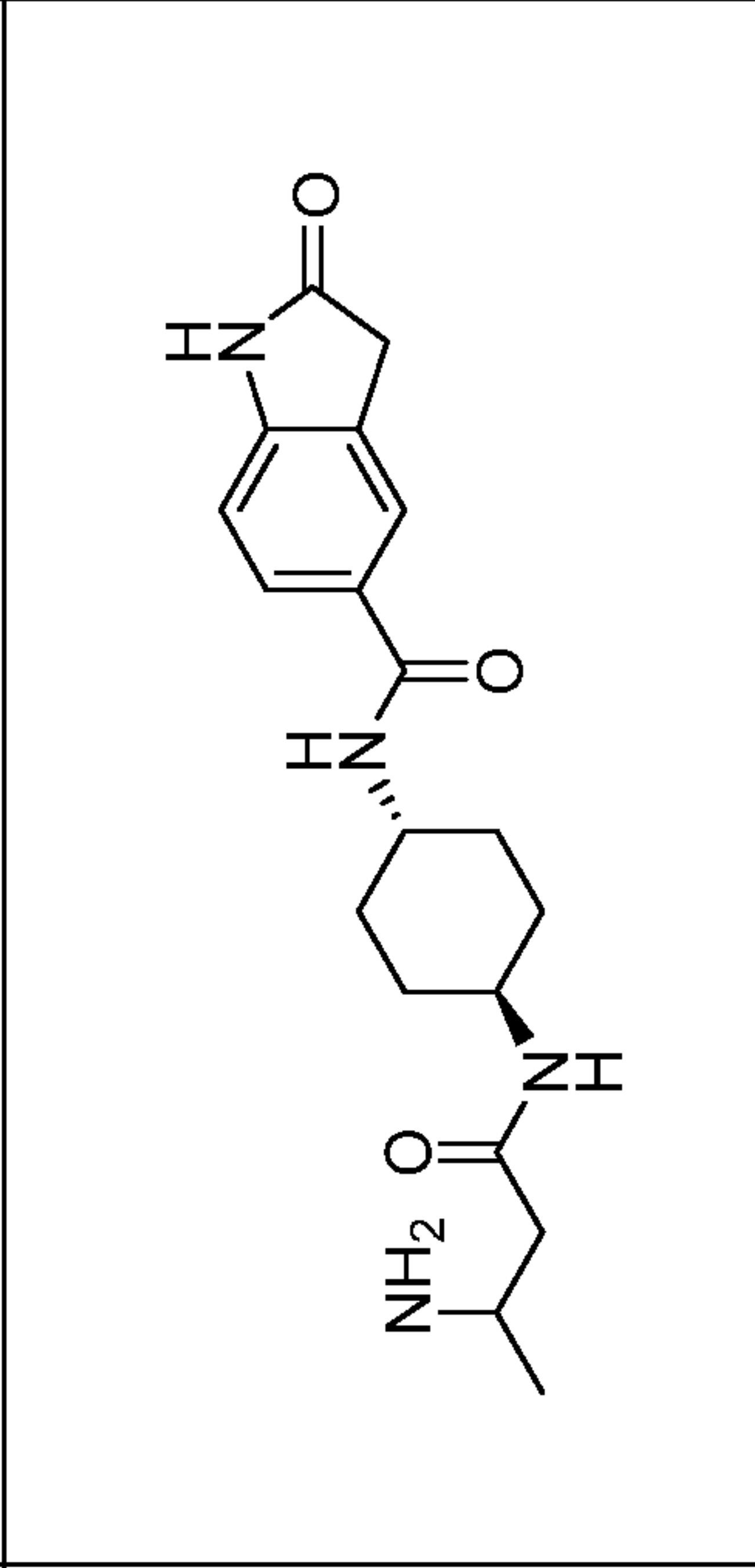
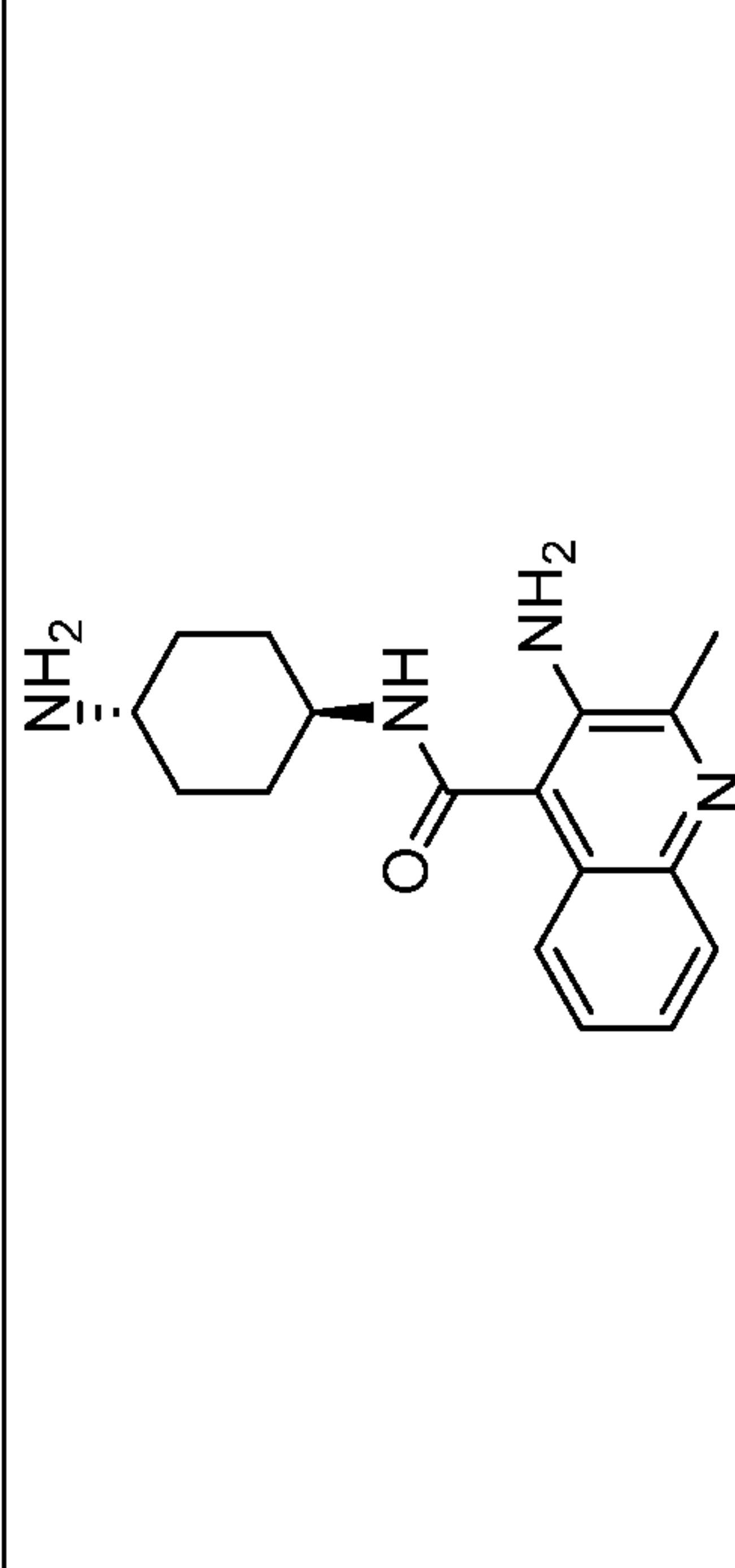
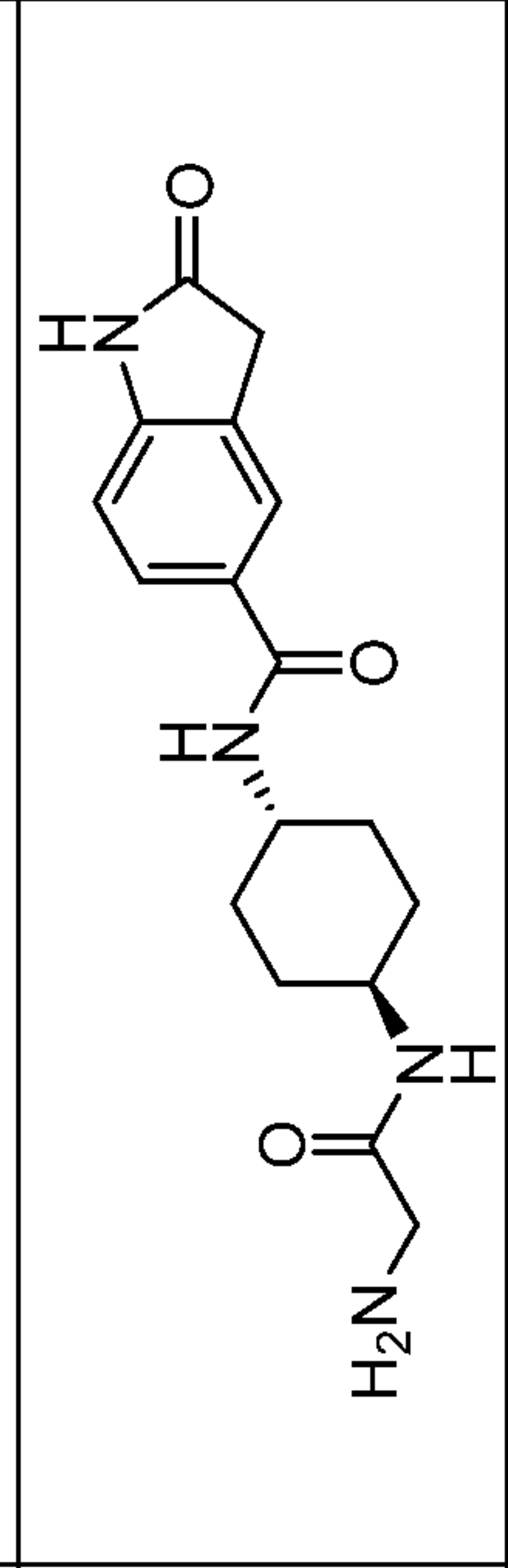
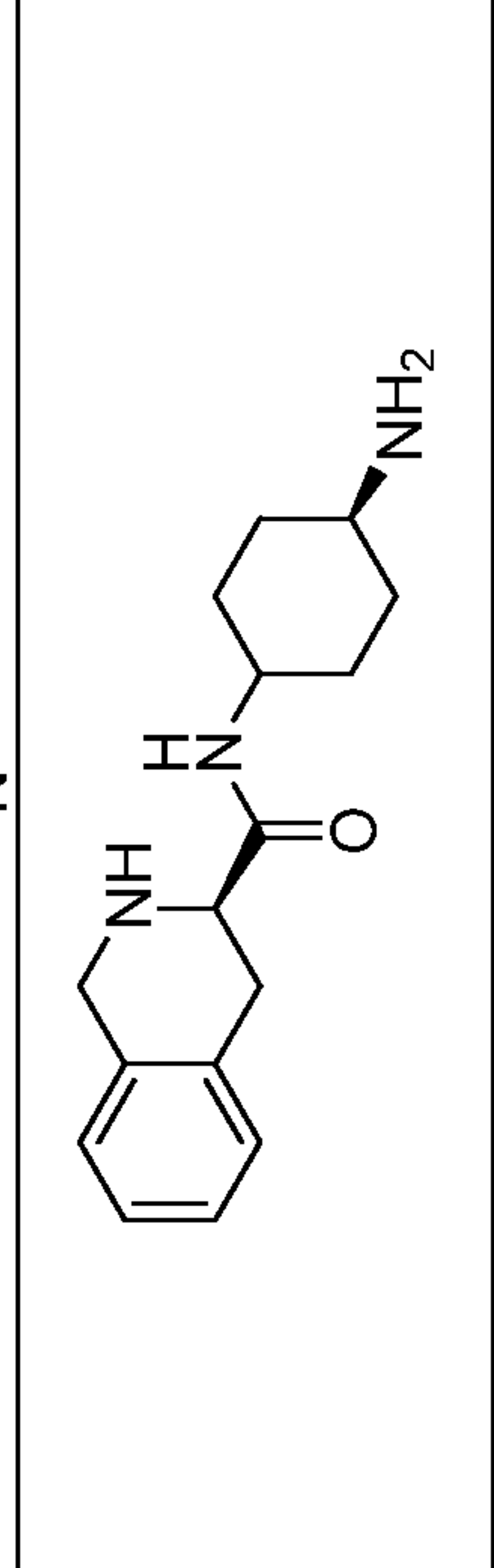
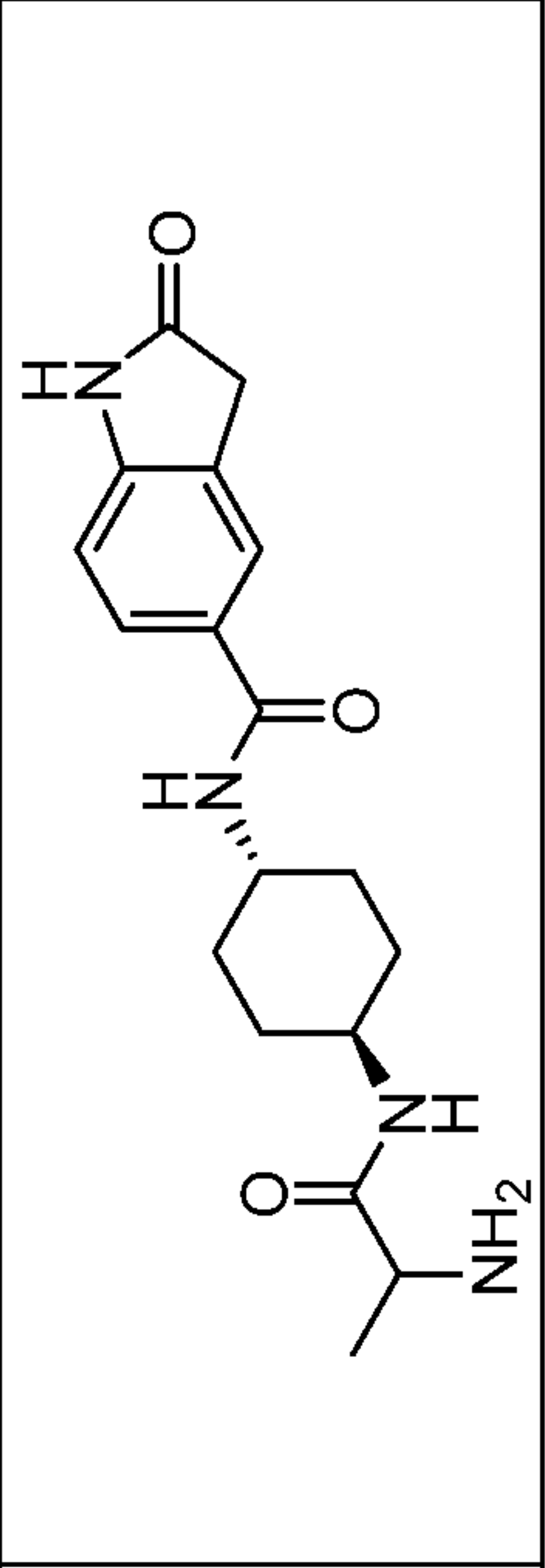
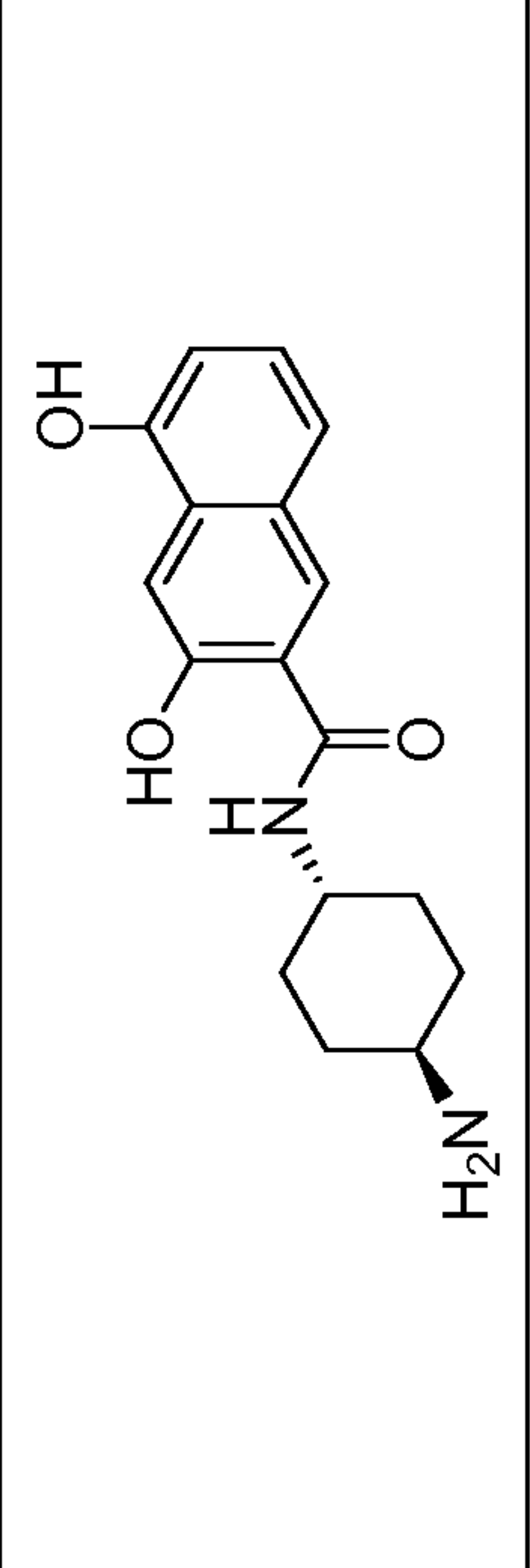
149		HCl	434		HCl
150		HCl	435		HCl
151		HCl	436		TFA
152		HCl	437		None
153		HCl	438		TFA

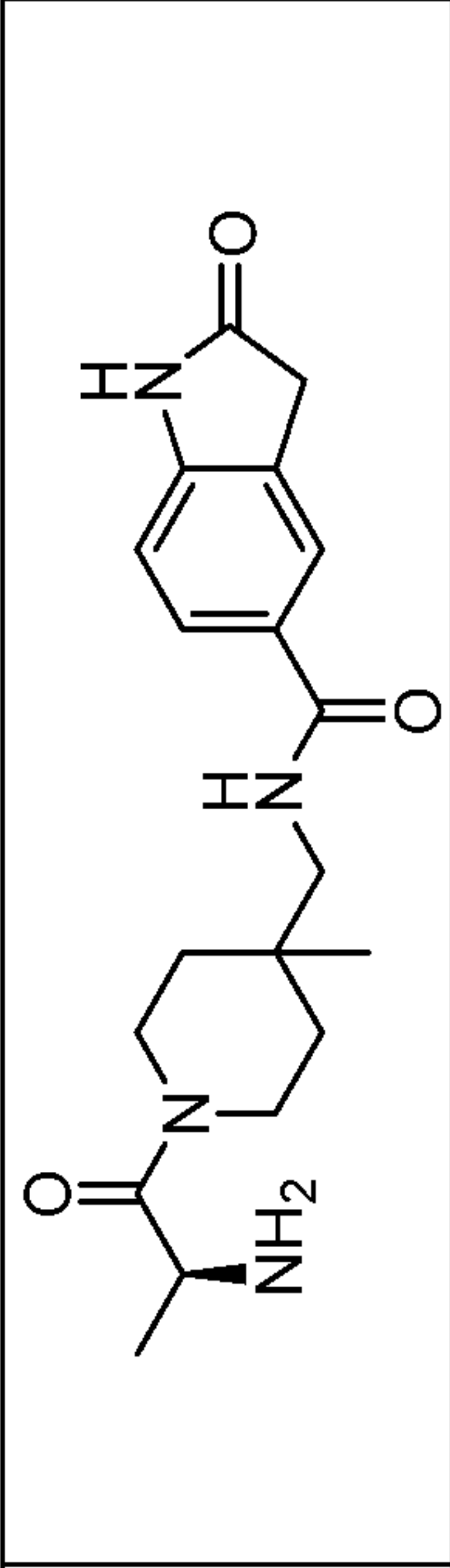
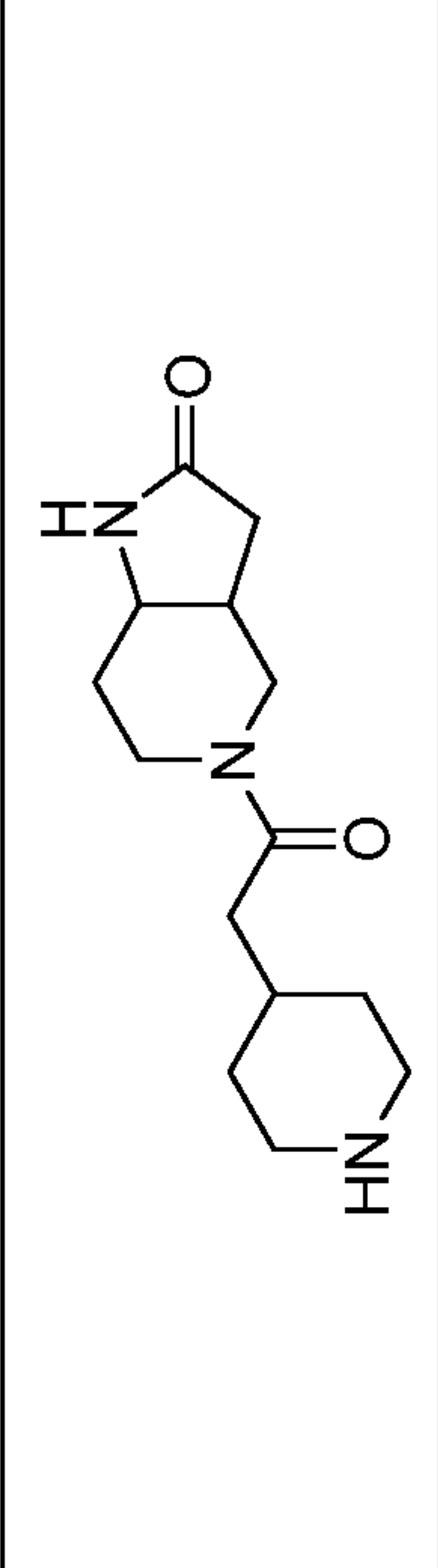
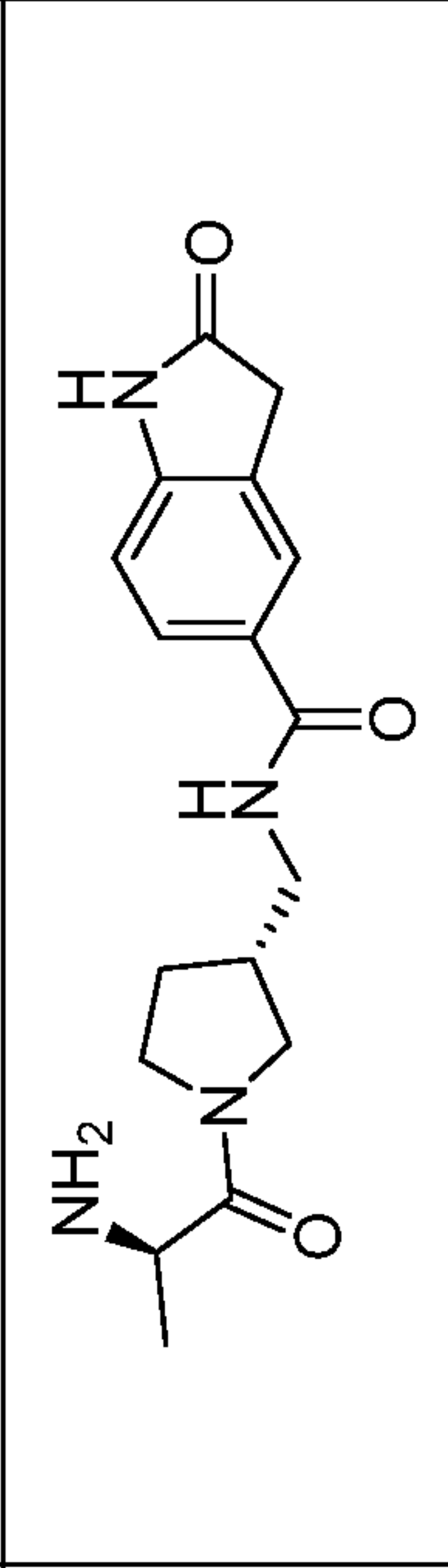
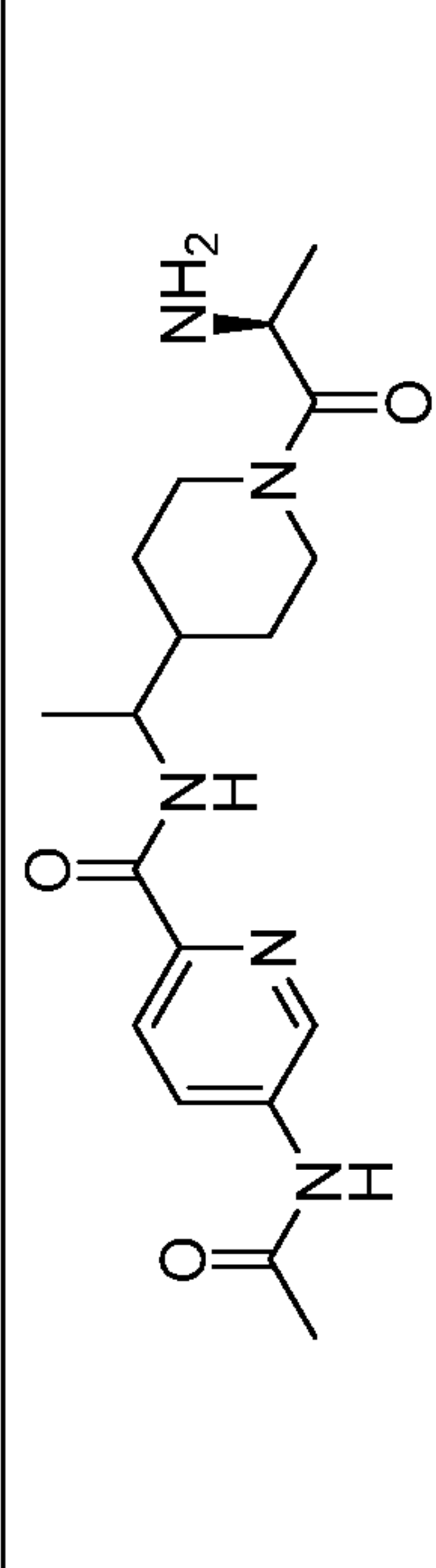
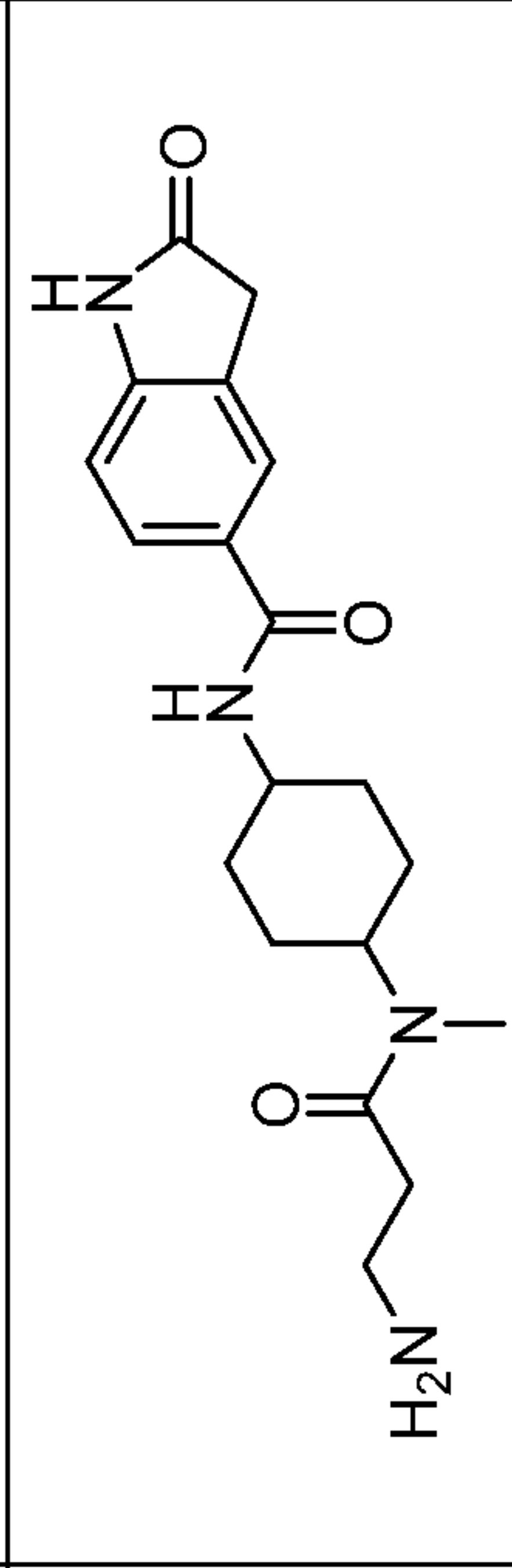
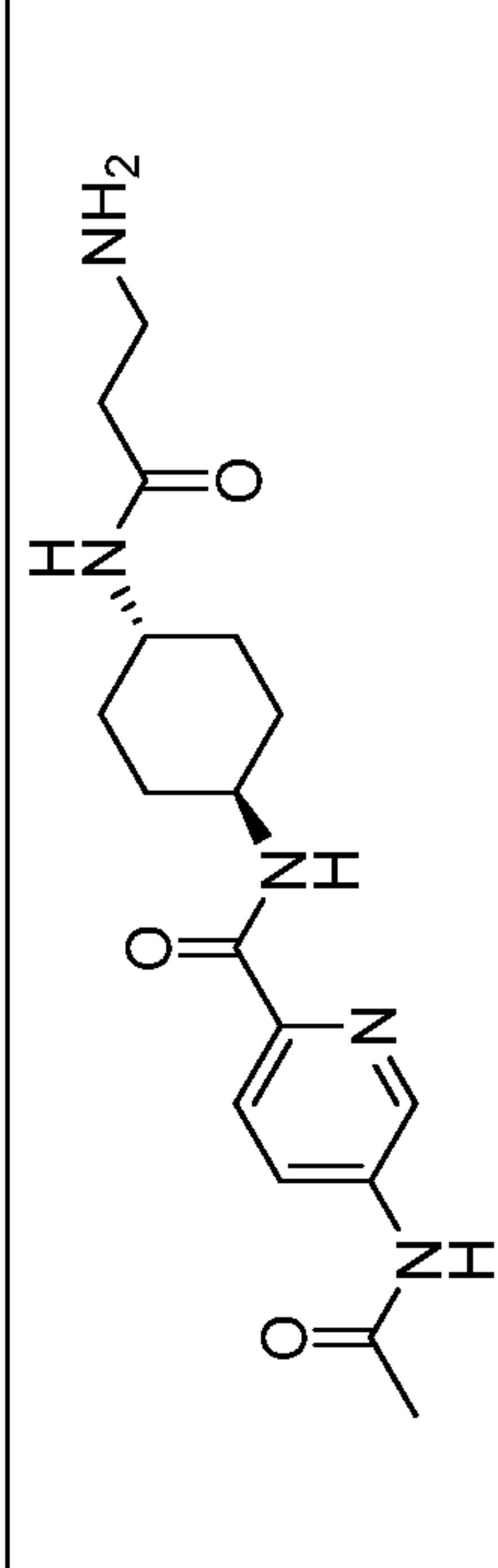
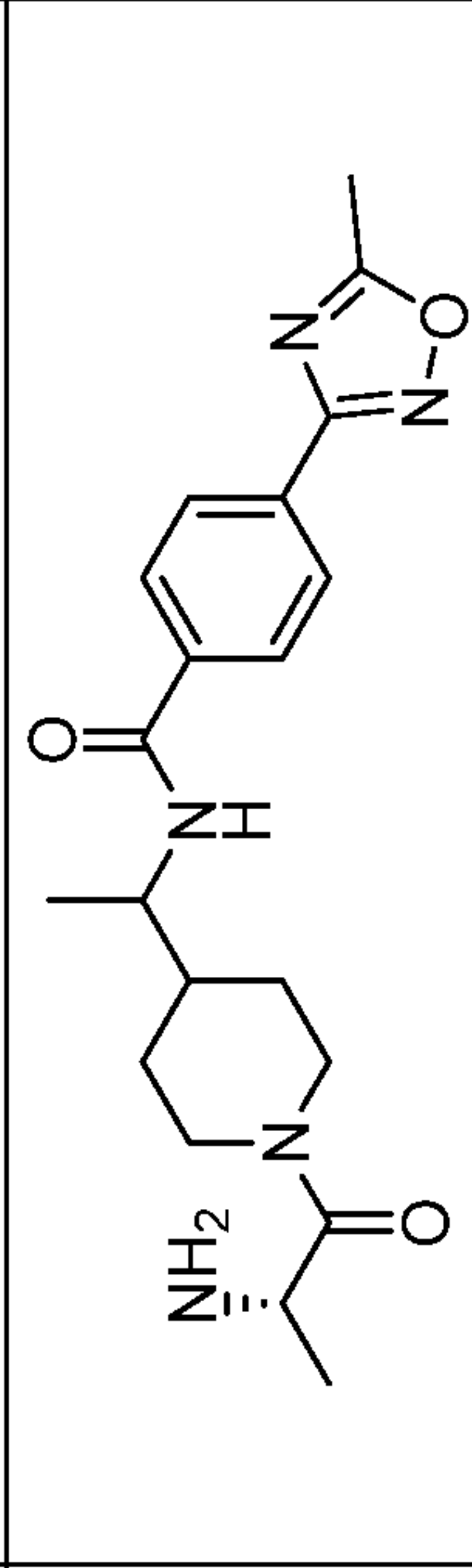
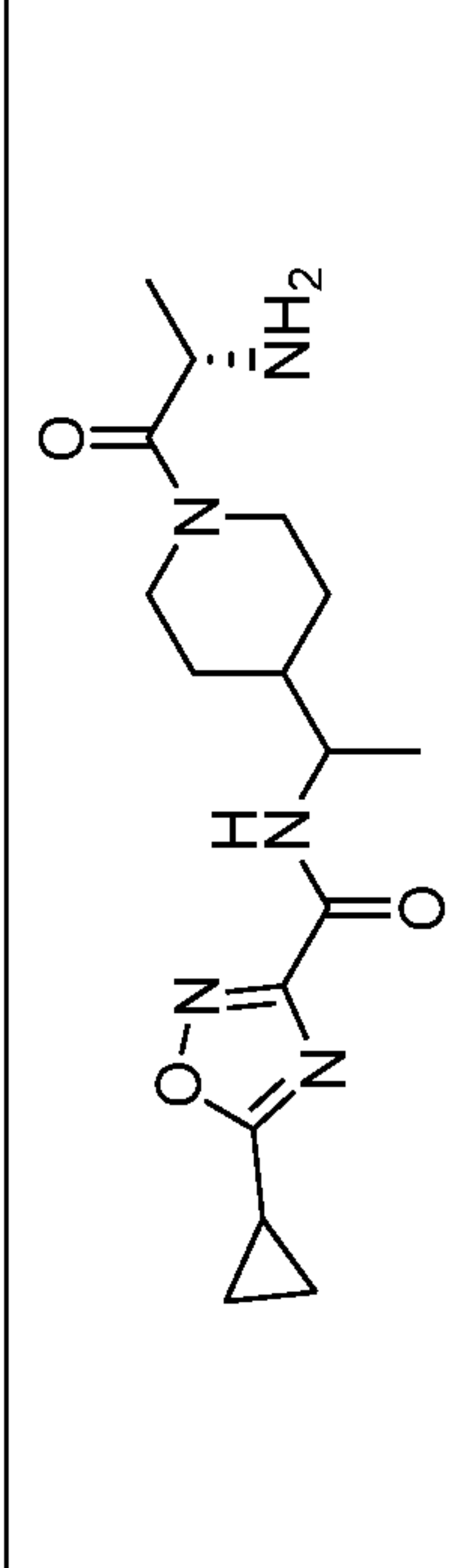
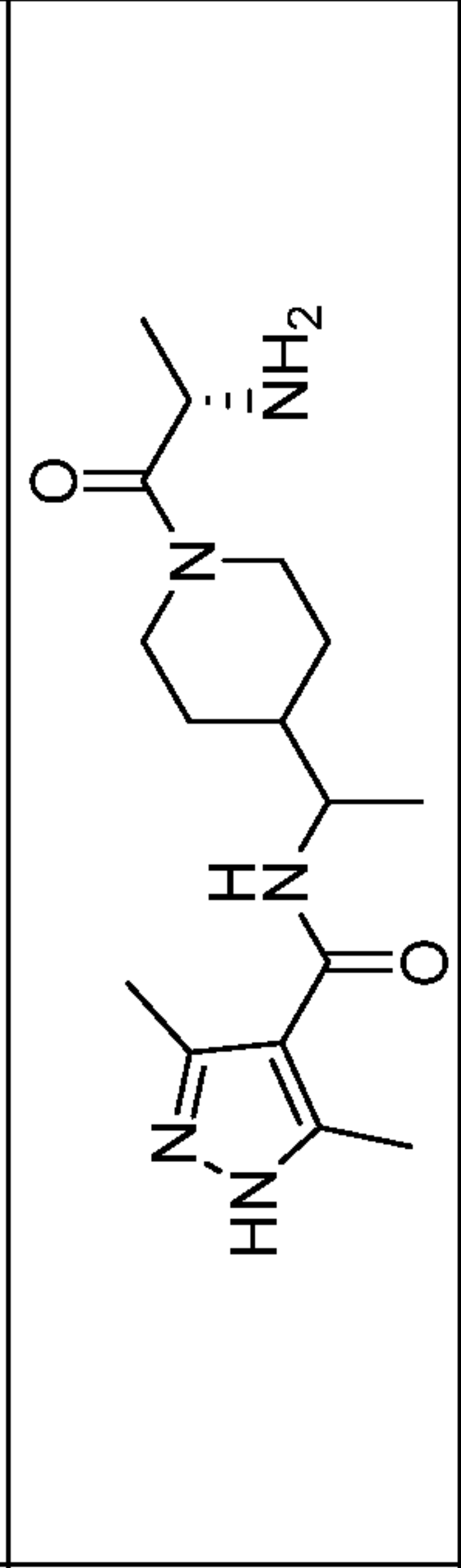
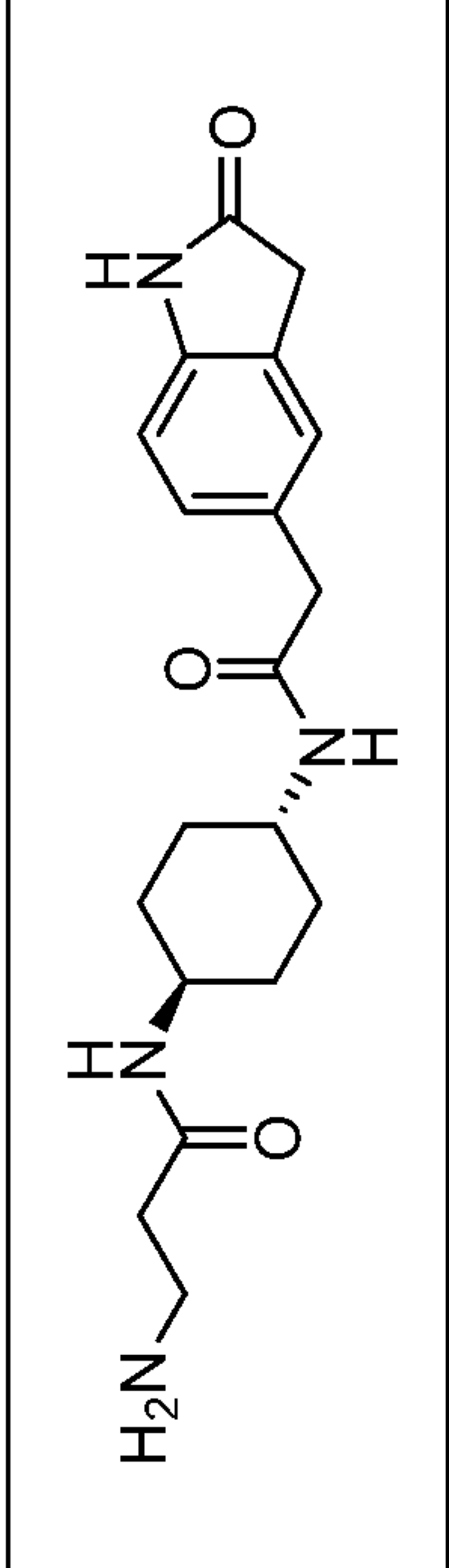
154		HCl	439		HCl
155		HCl	440		HCl
156		HCl	441		TFA
157		HCl	442		HCl

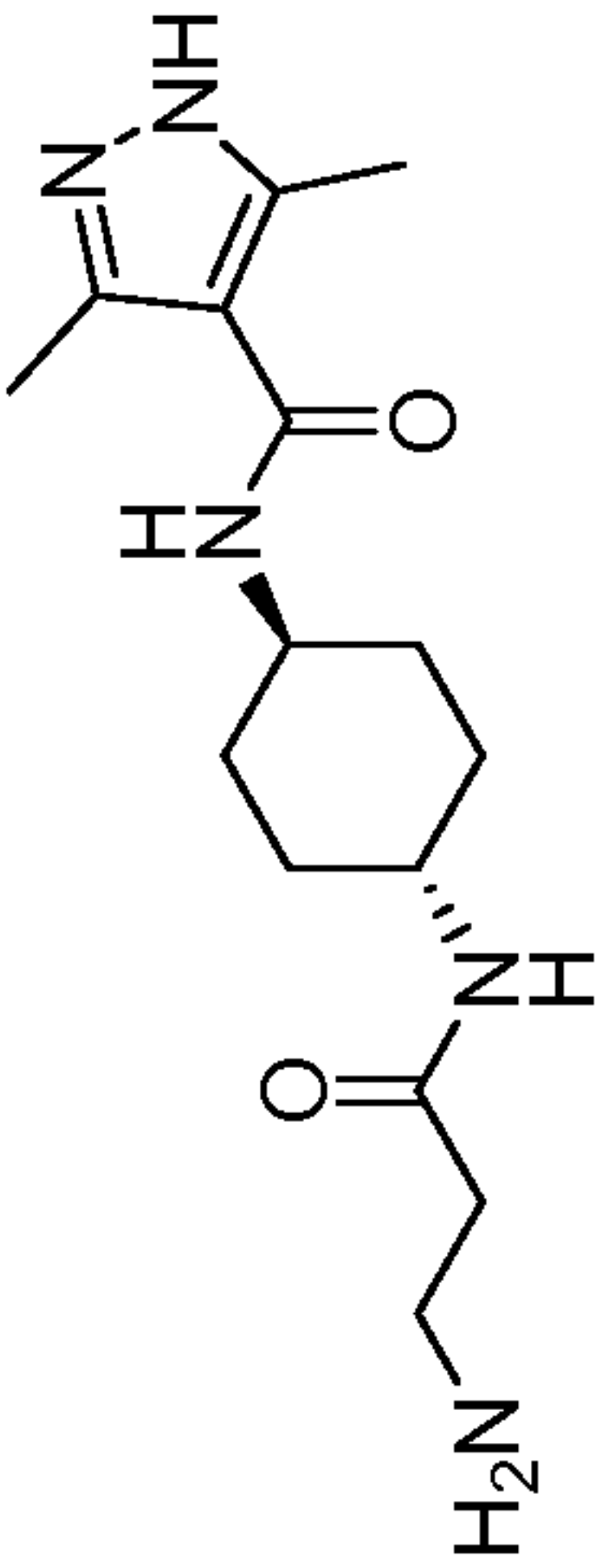
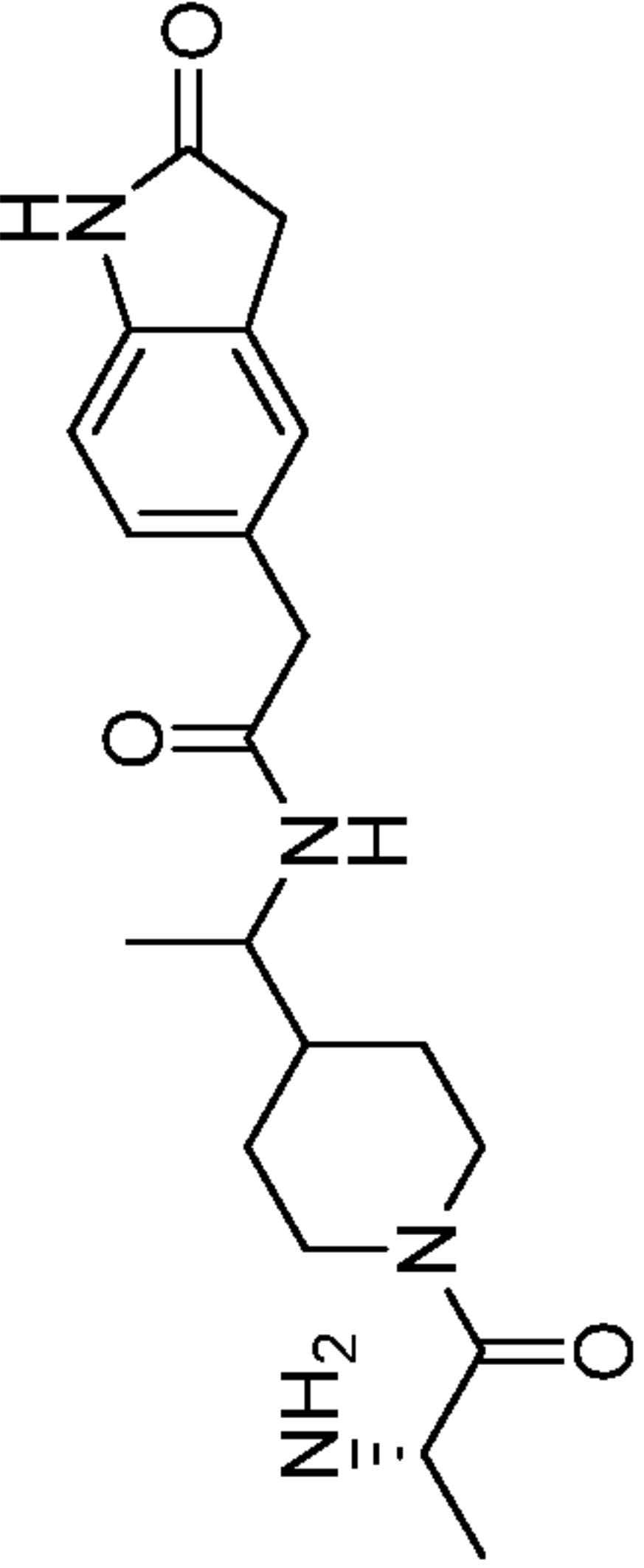
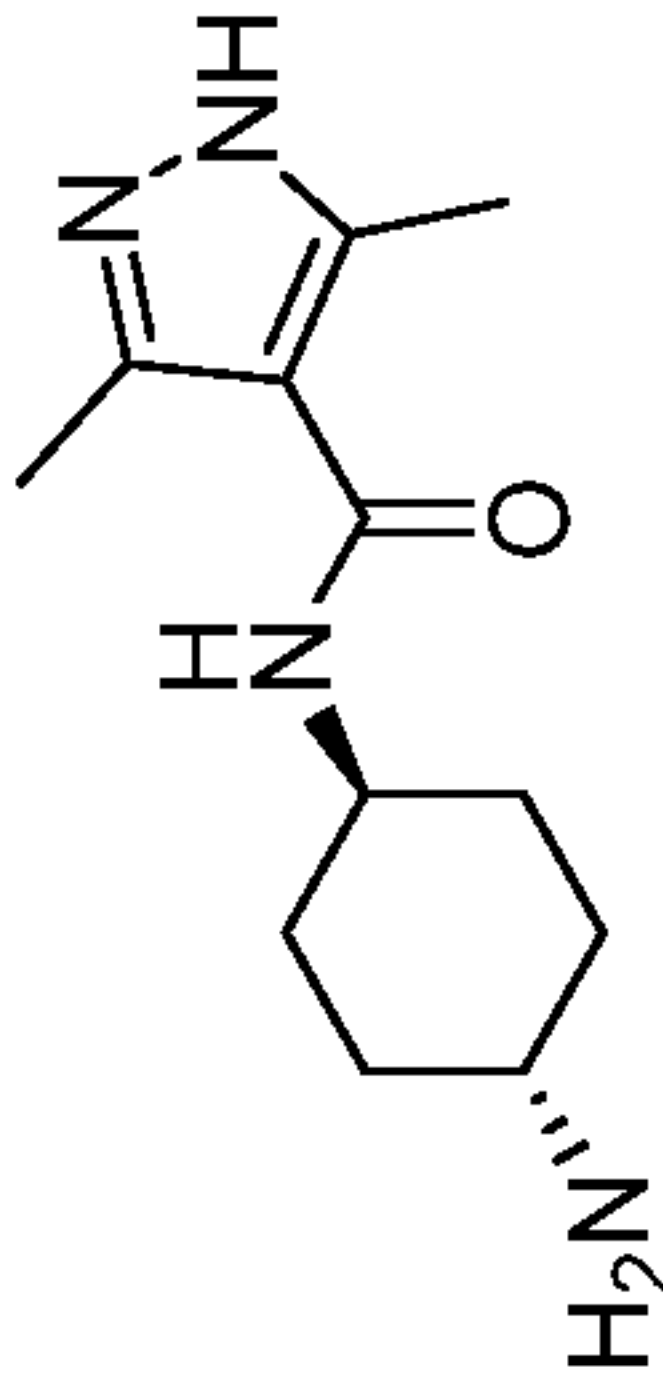
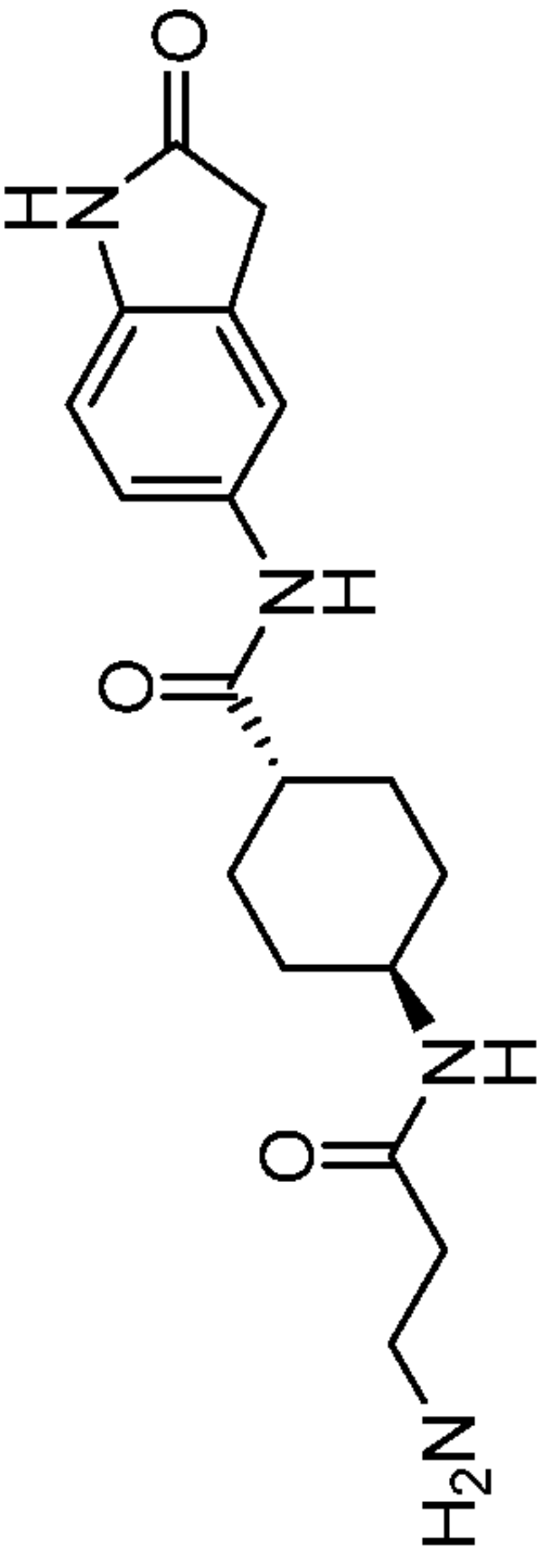
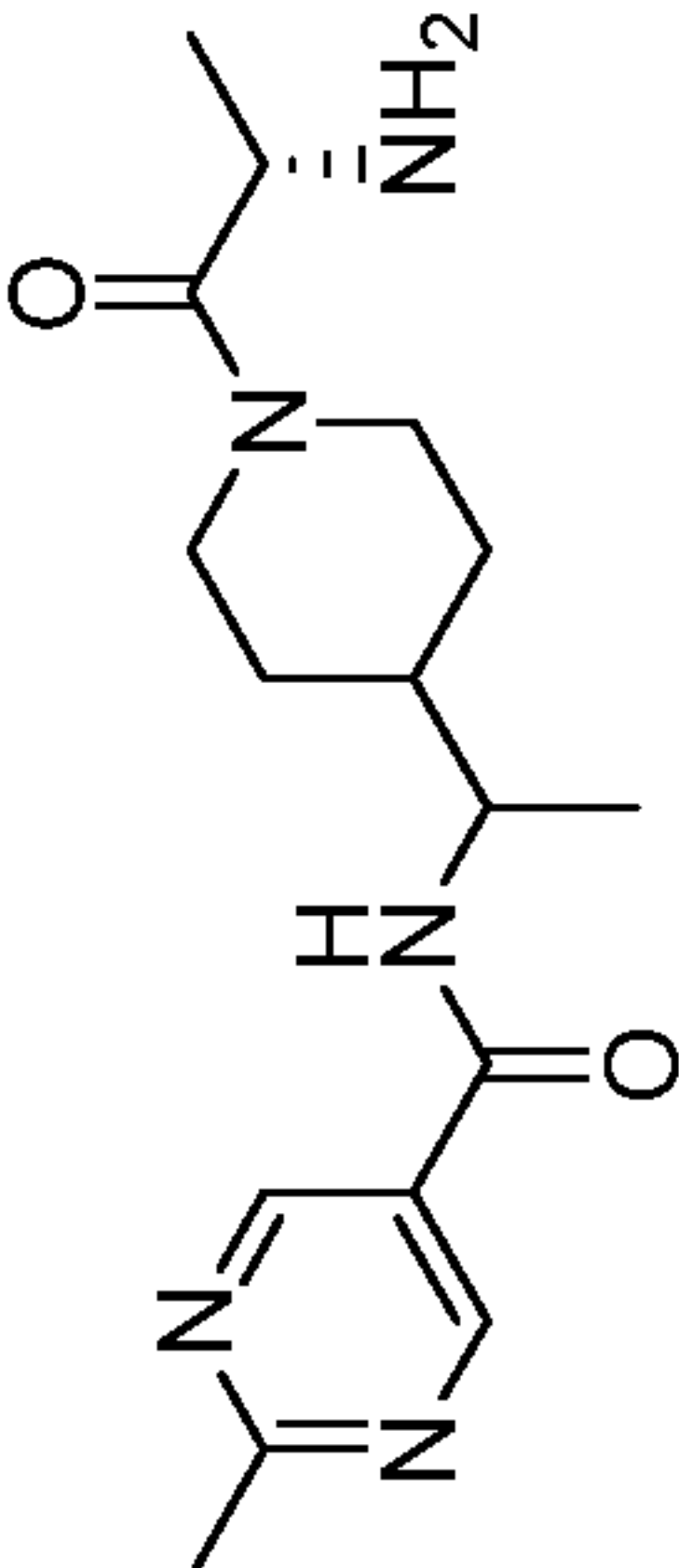
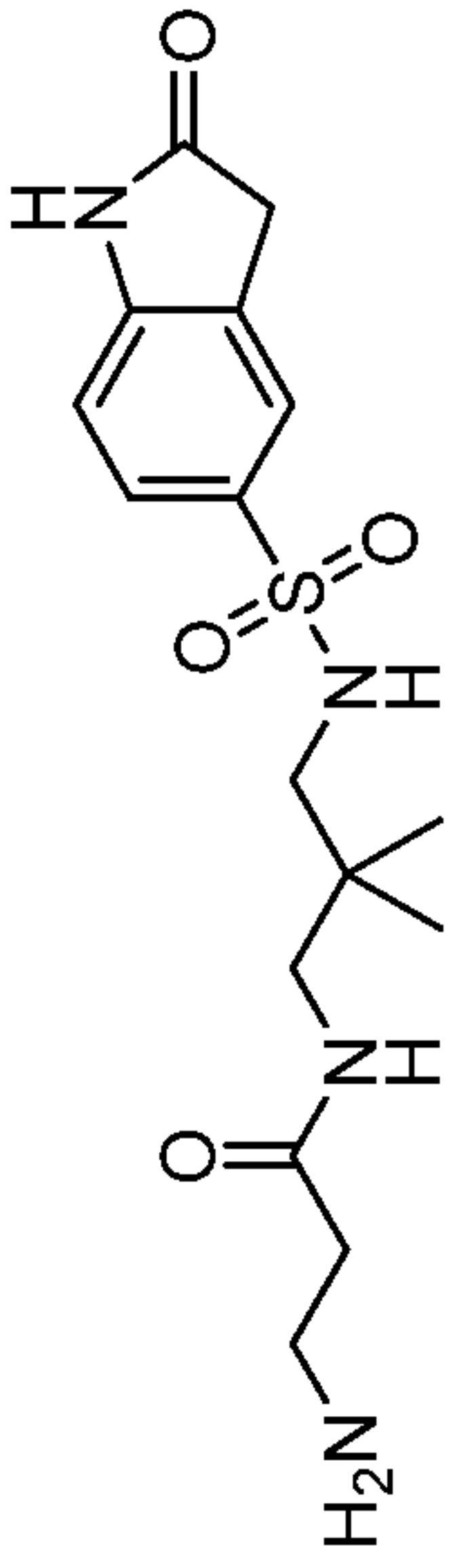
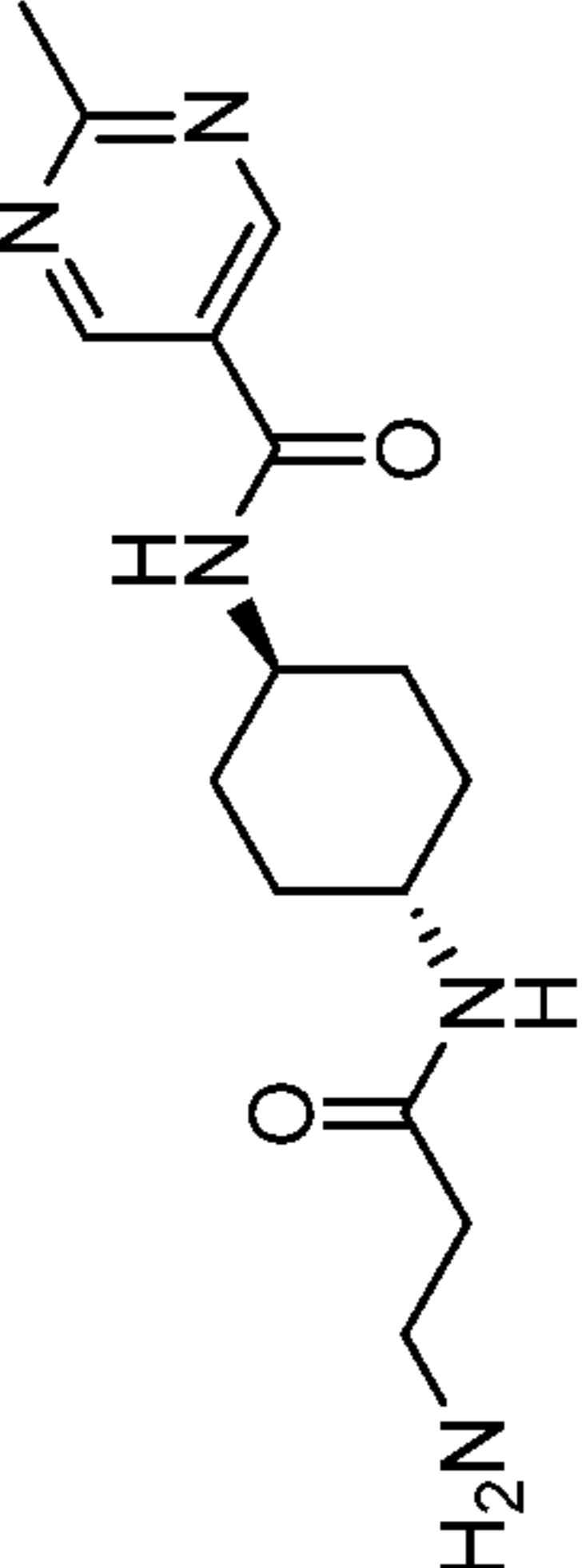
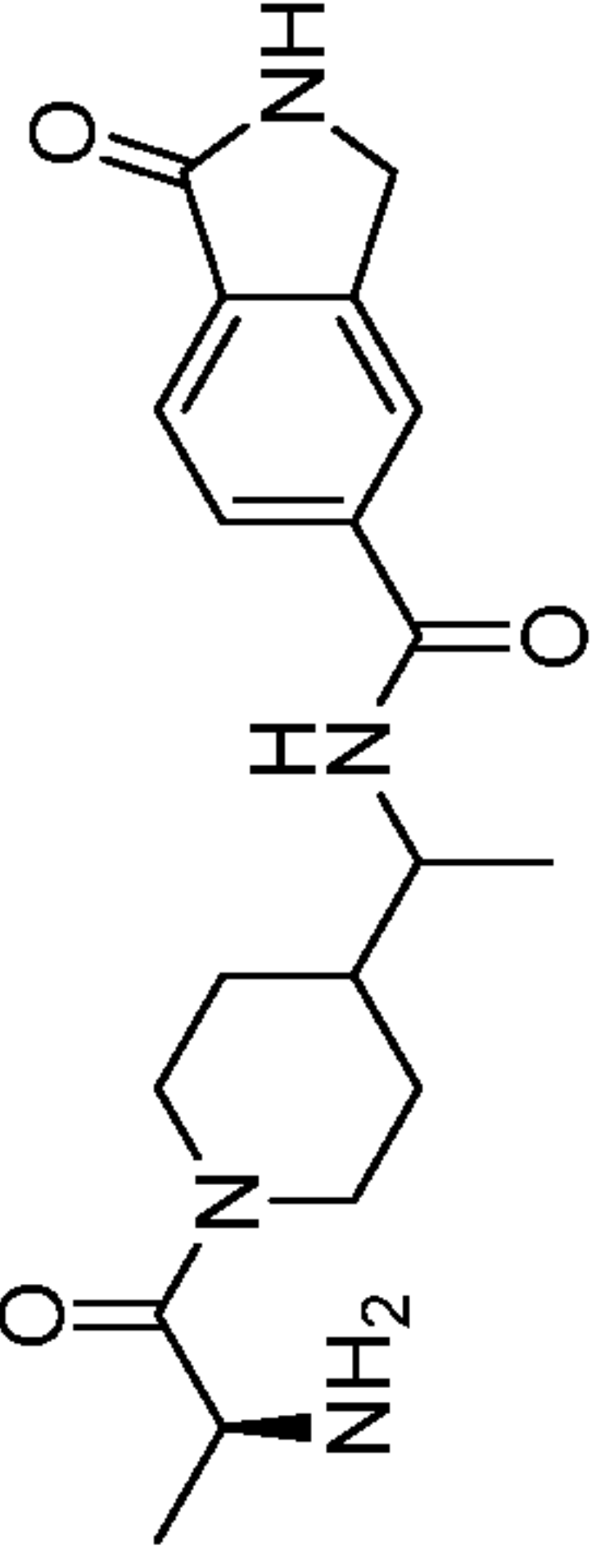
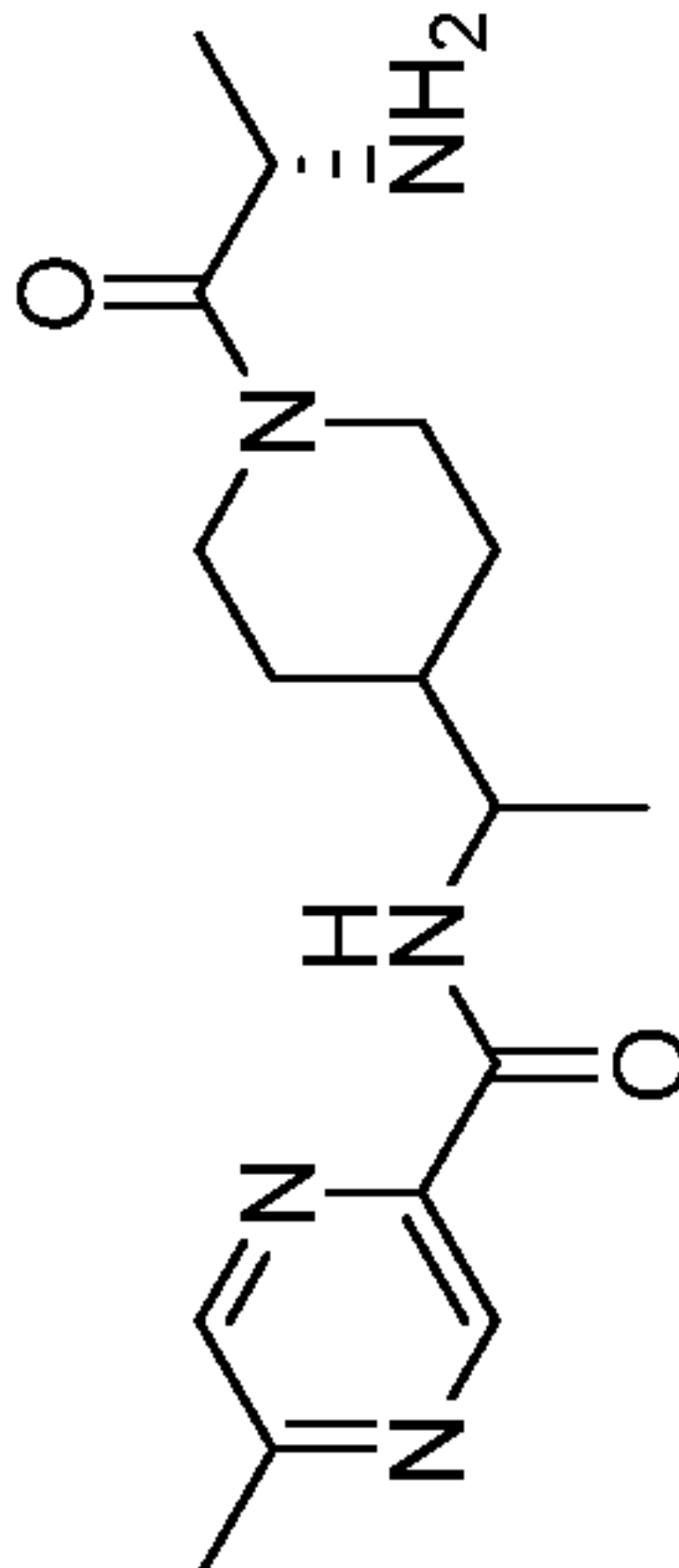
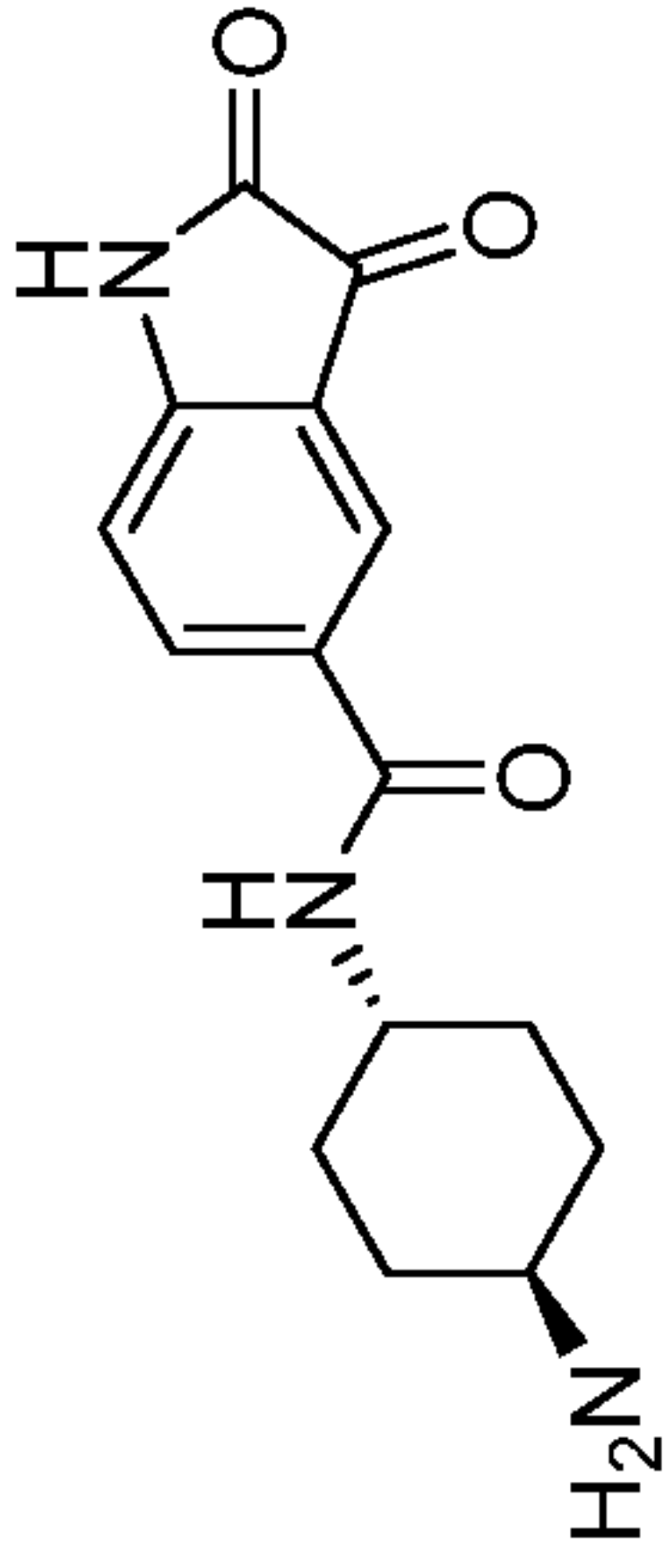
158		HCl	443		HCl
159		HCl	444		TFA
160		HCl	445		TFA
161		HCl	446		TFA
162		HCl	447		TFA

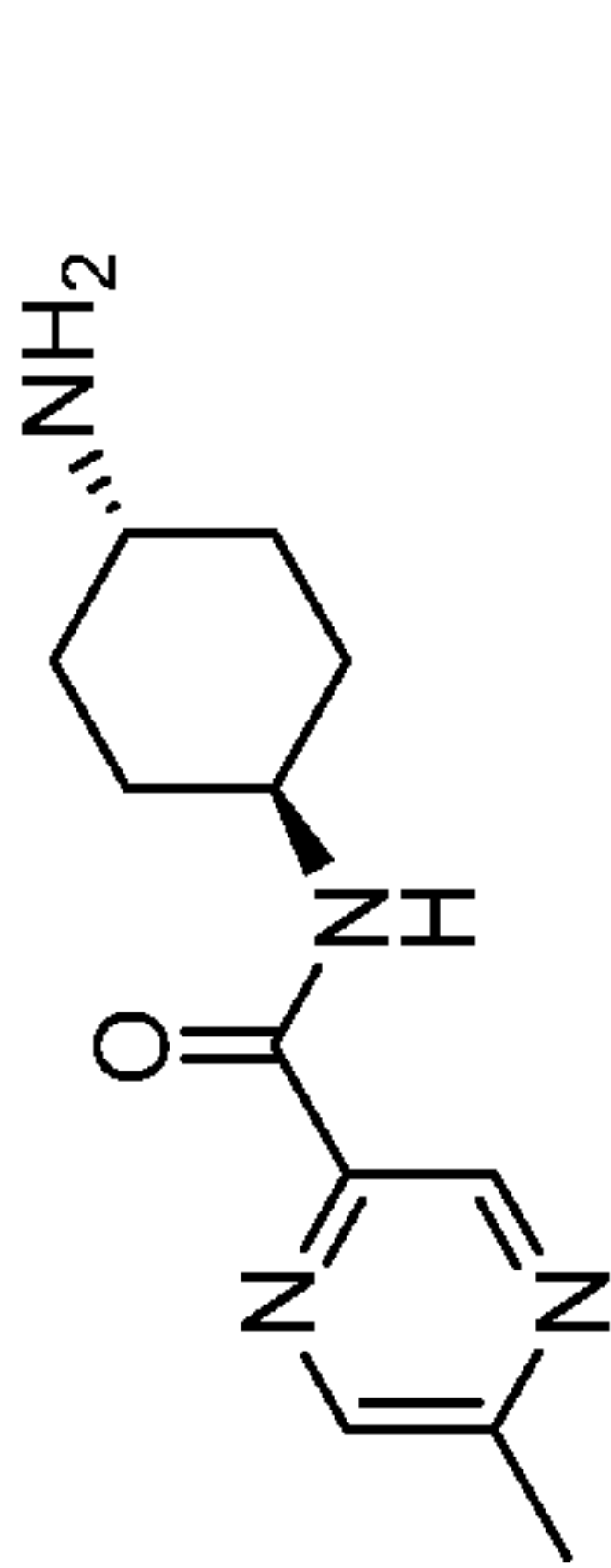
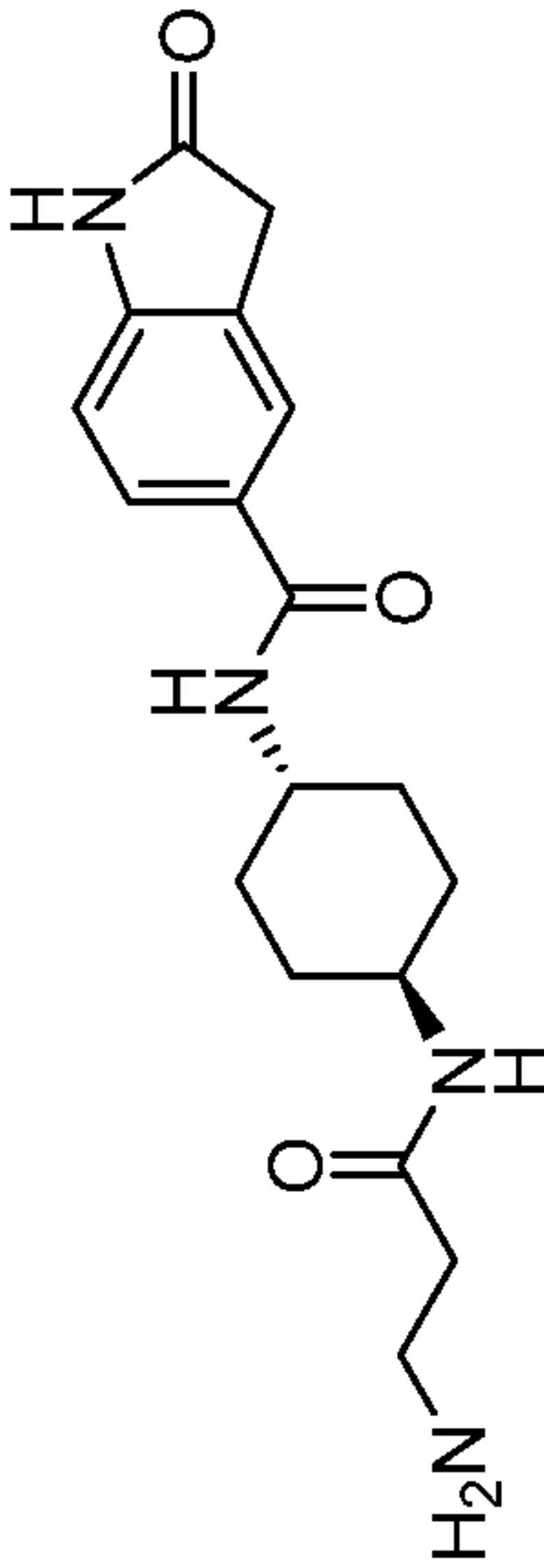
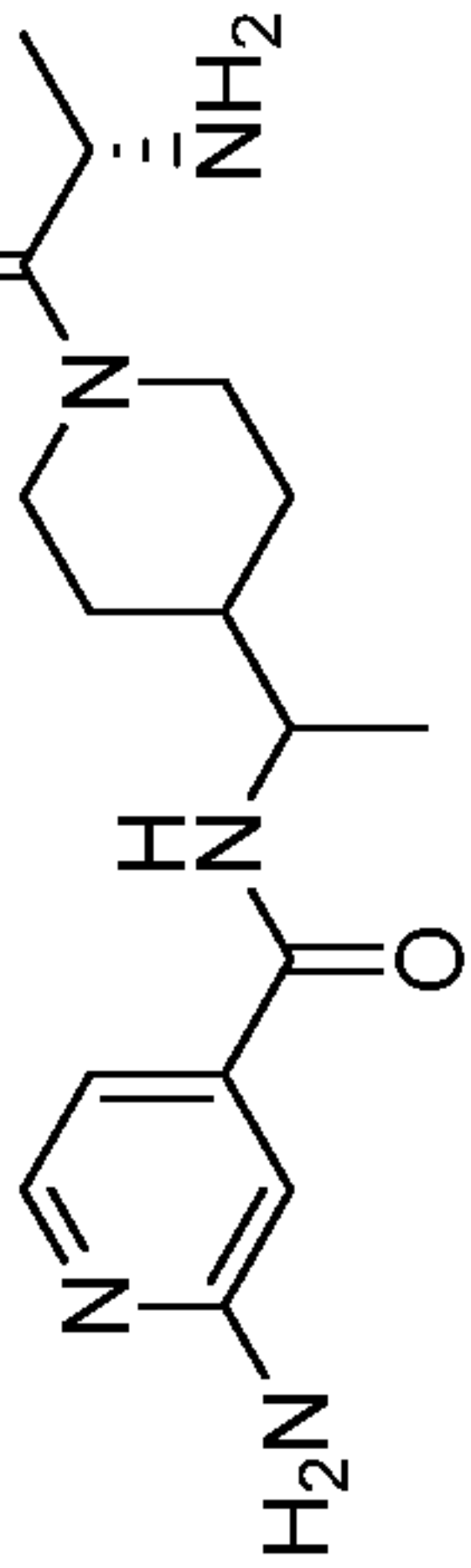
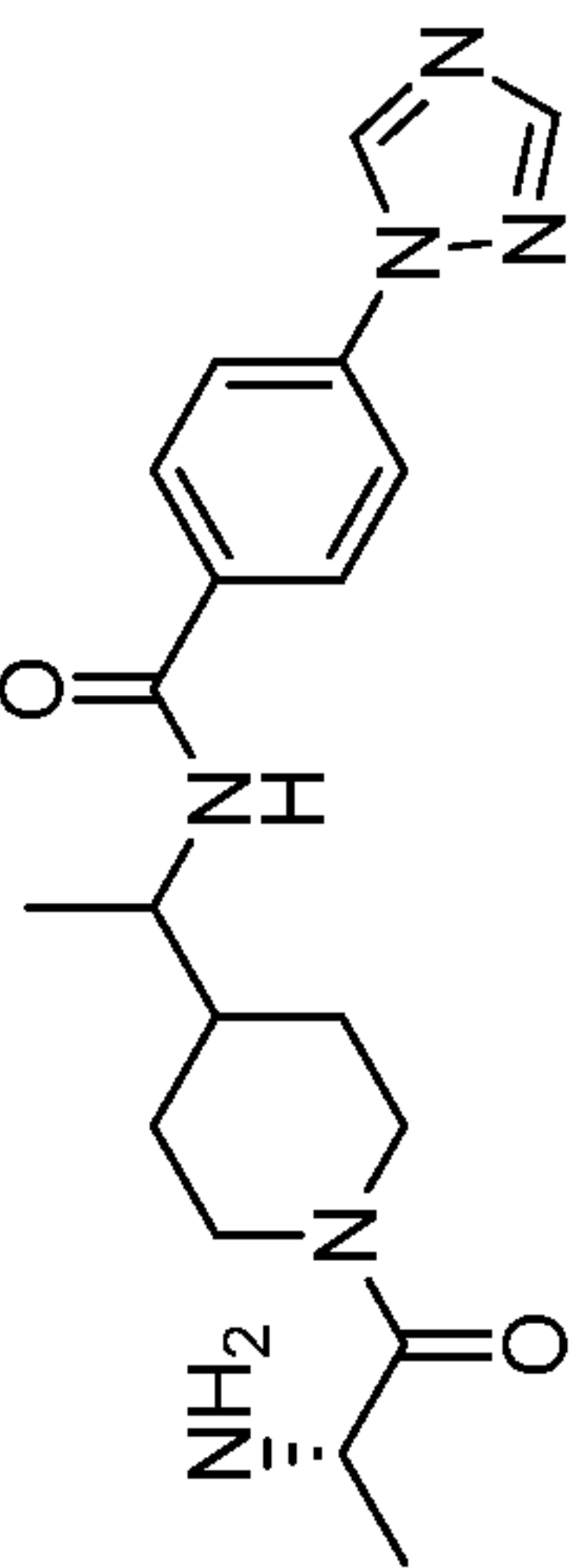
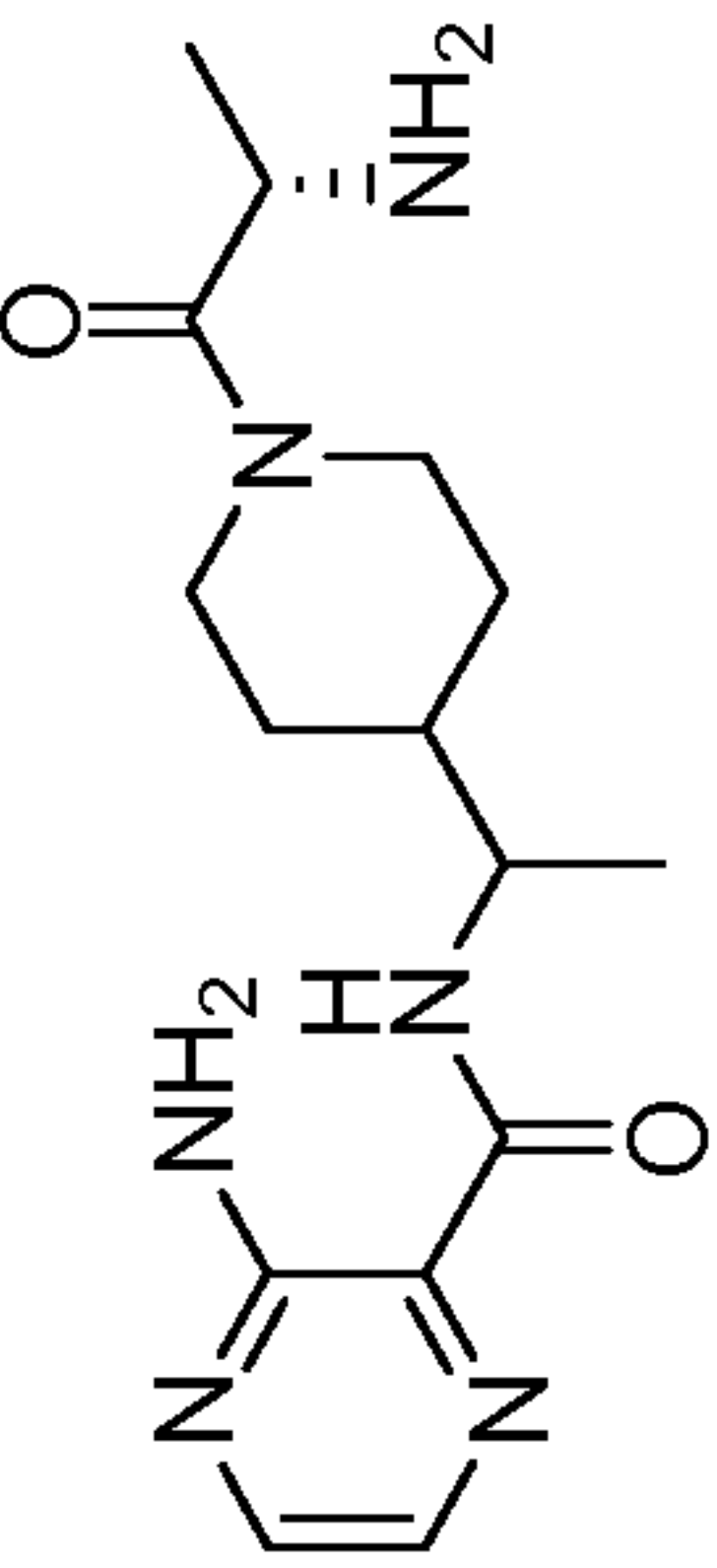
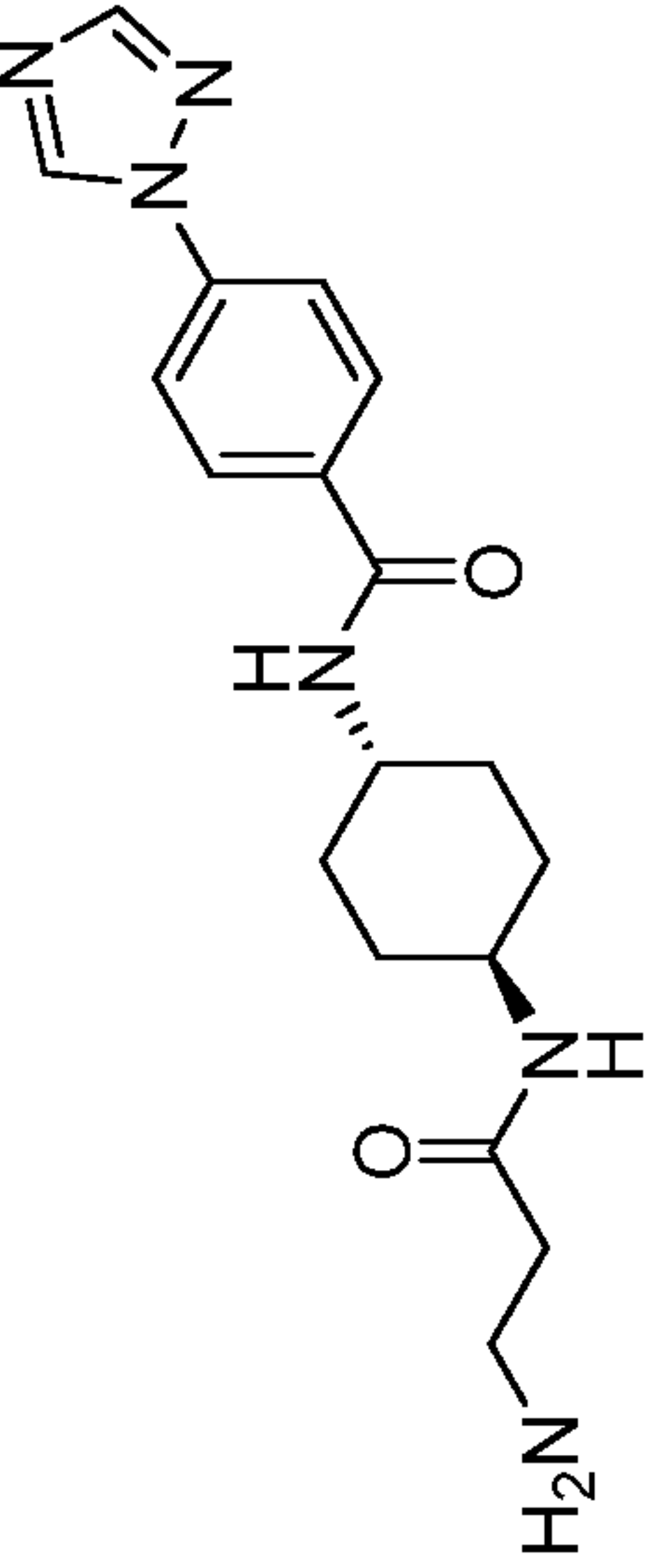
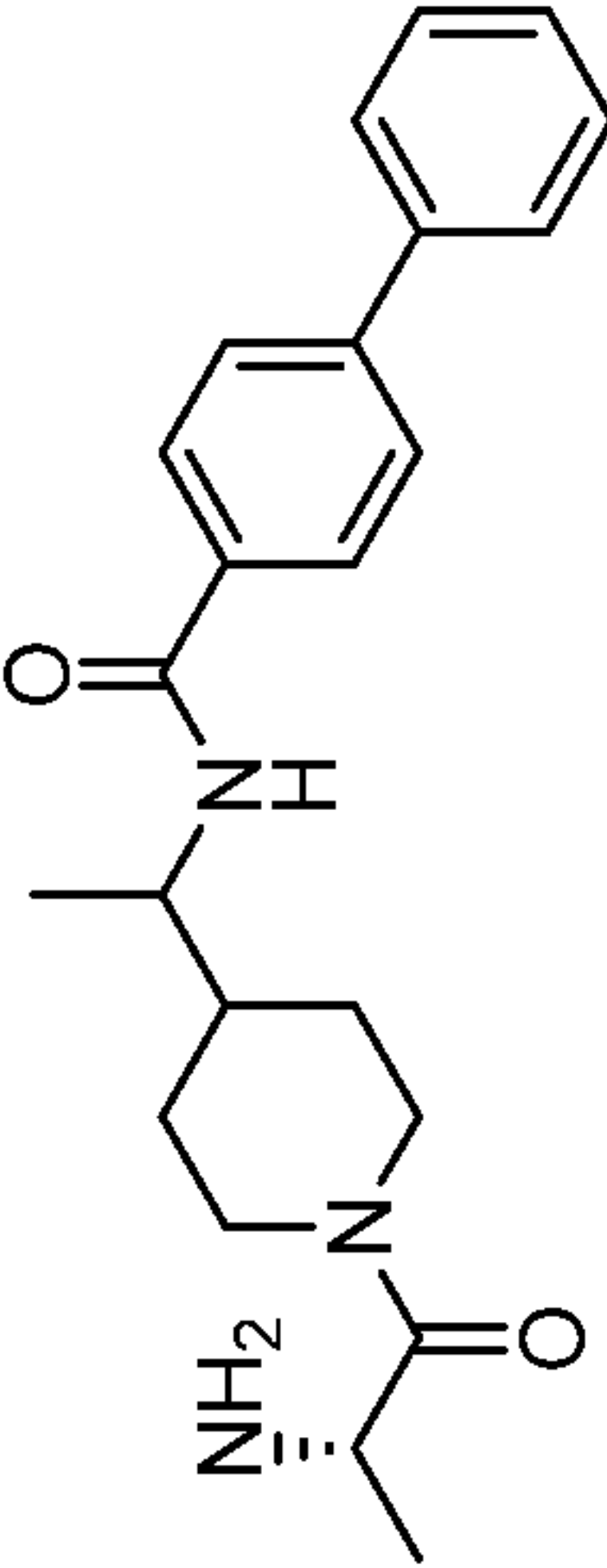
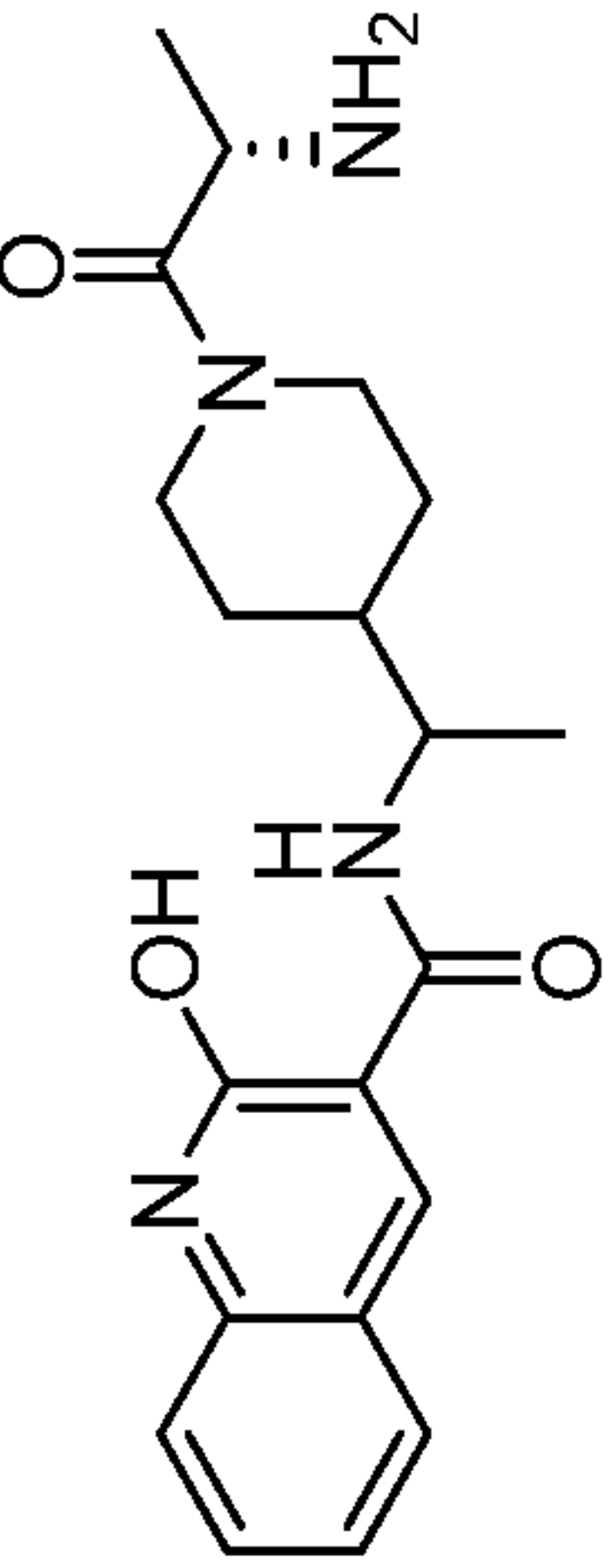
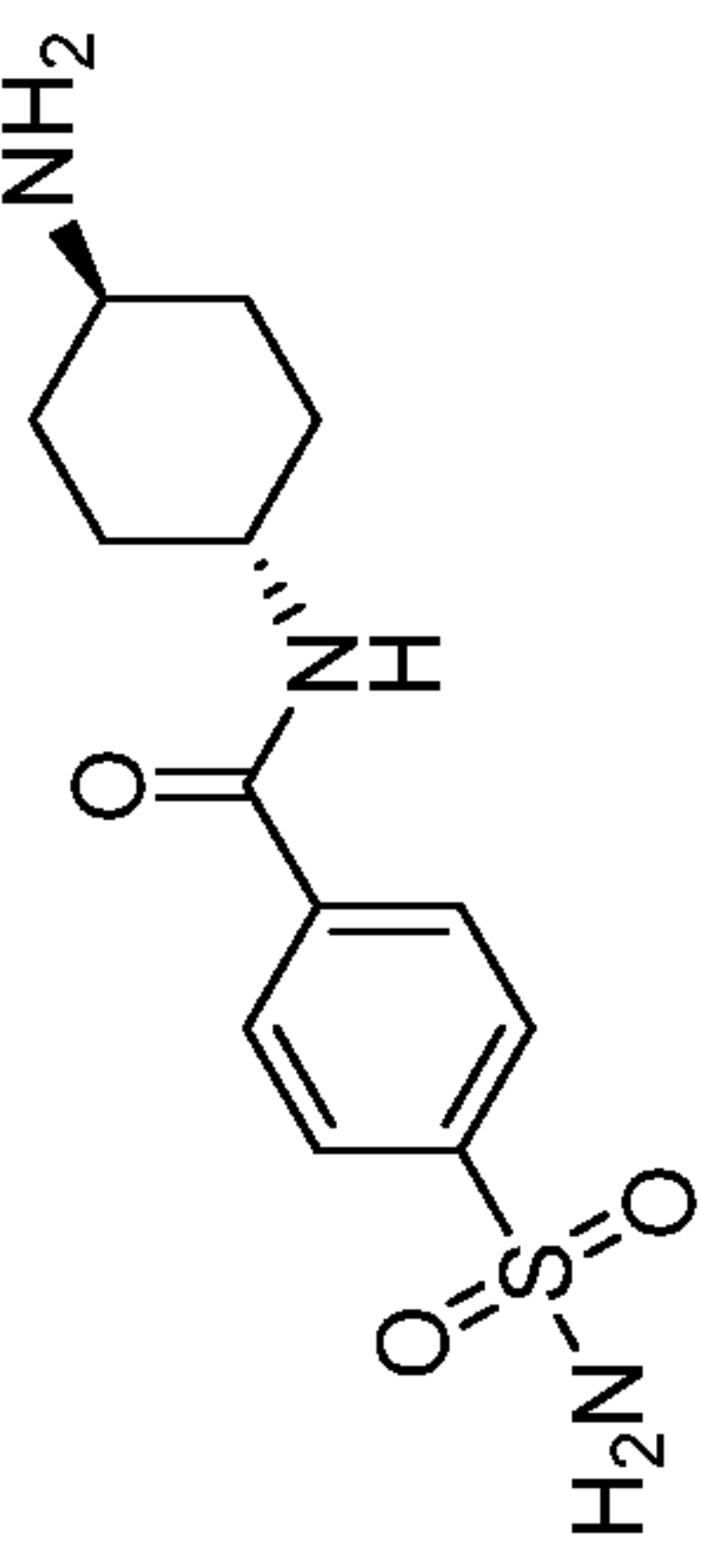
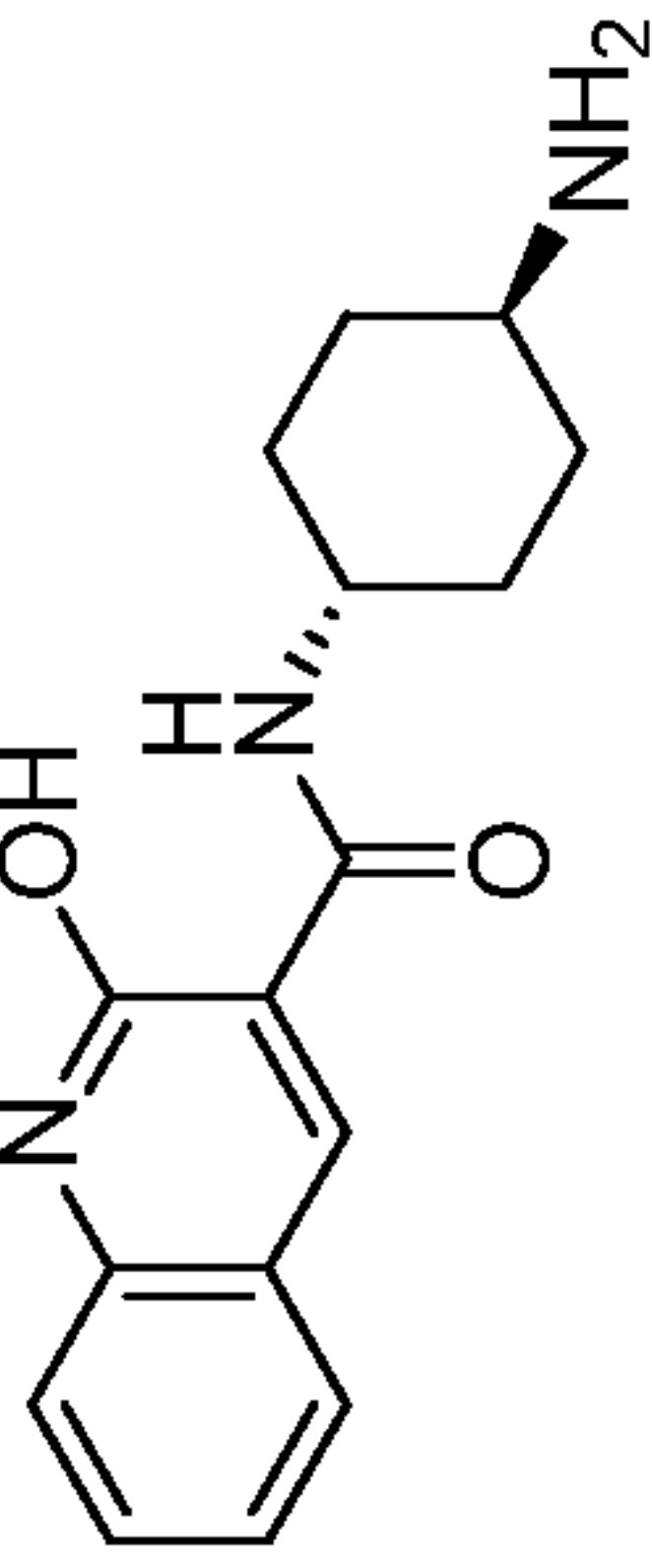
163		HCl	448		TFA
164		HCl	449		TFA
165		HCl	450		None
166		HCl	451		TFA
167		HCl	452		TFA

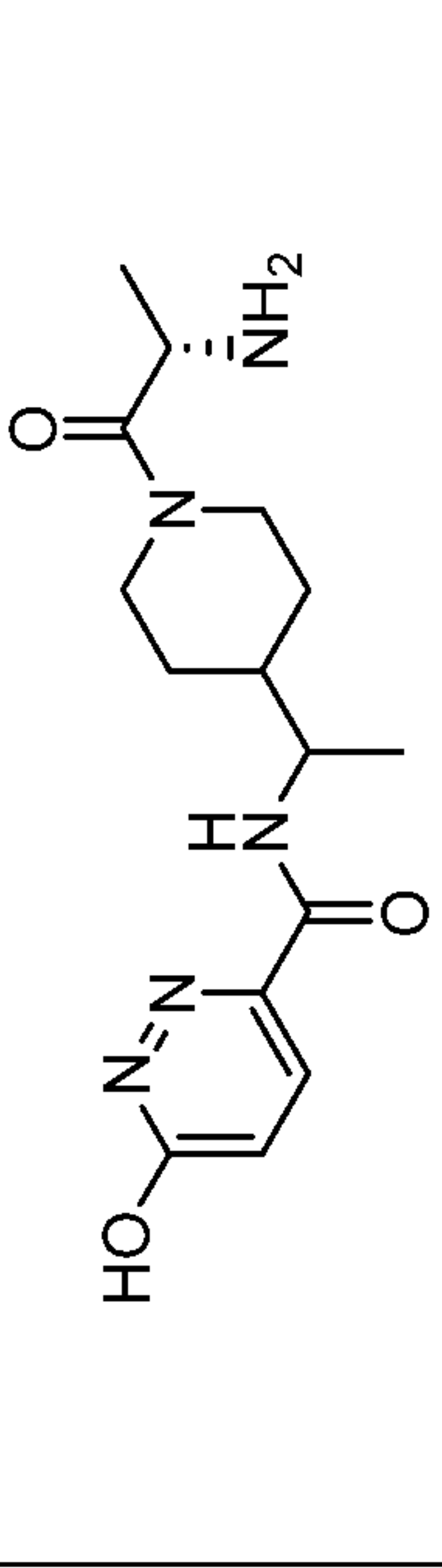
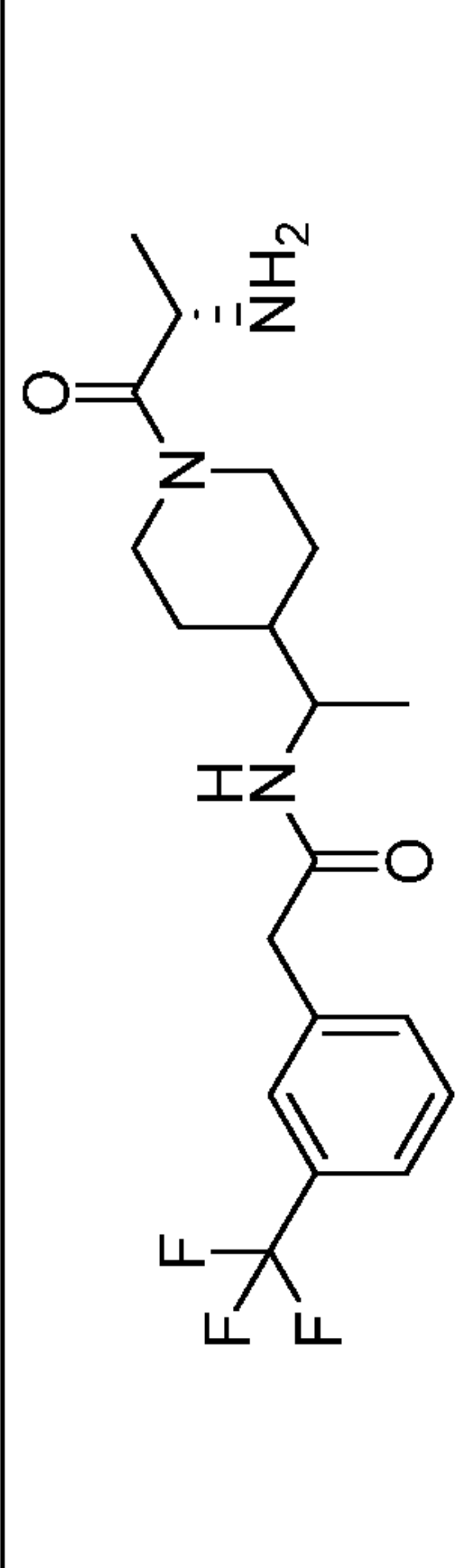
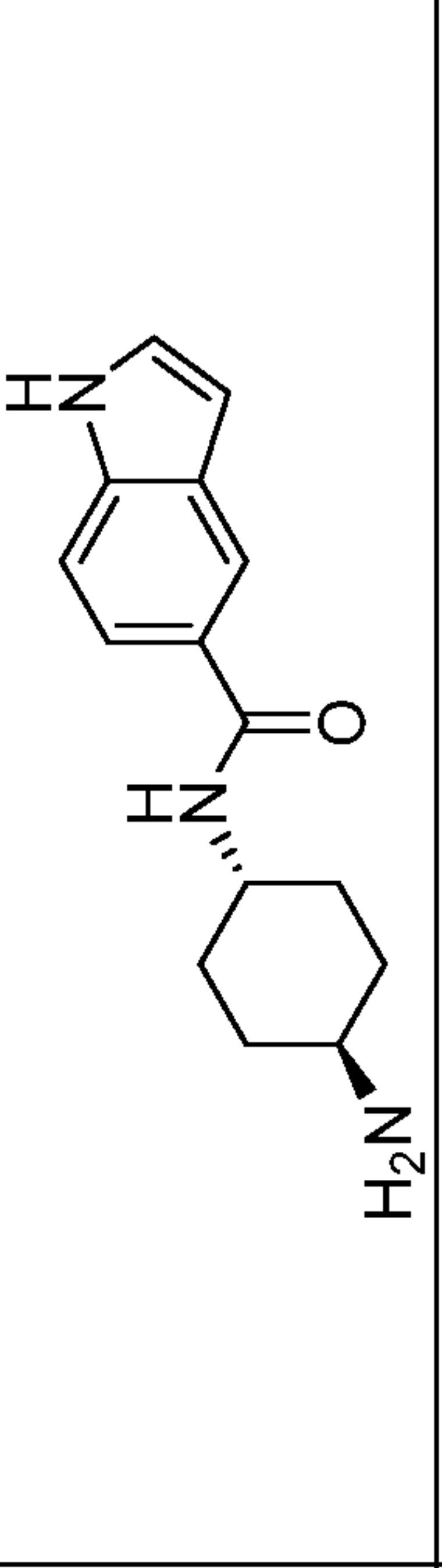
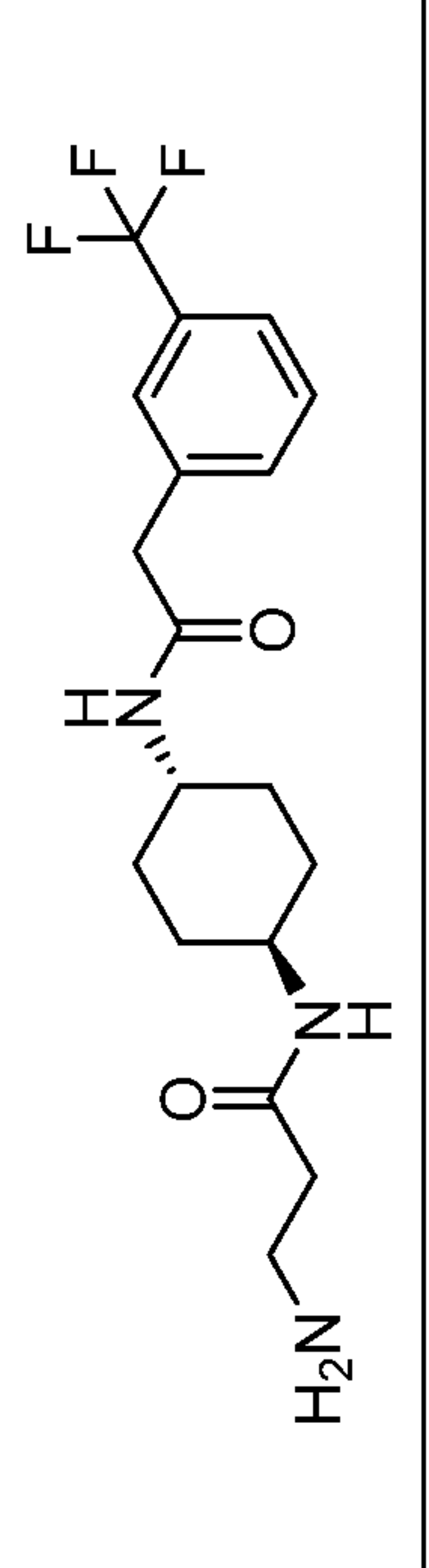
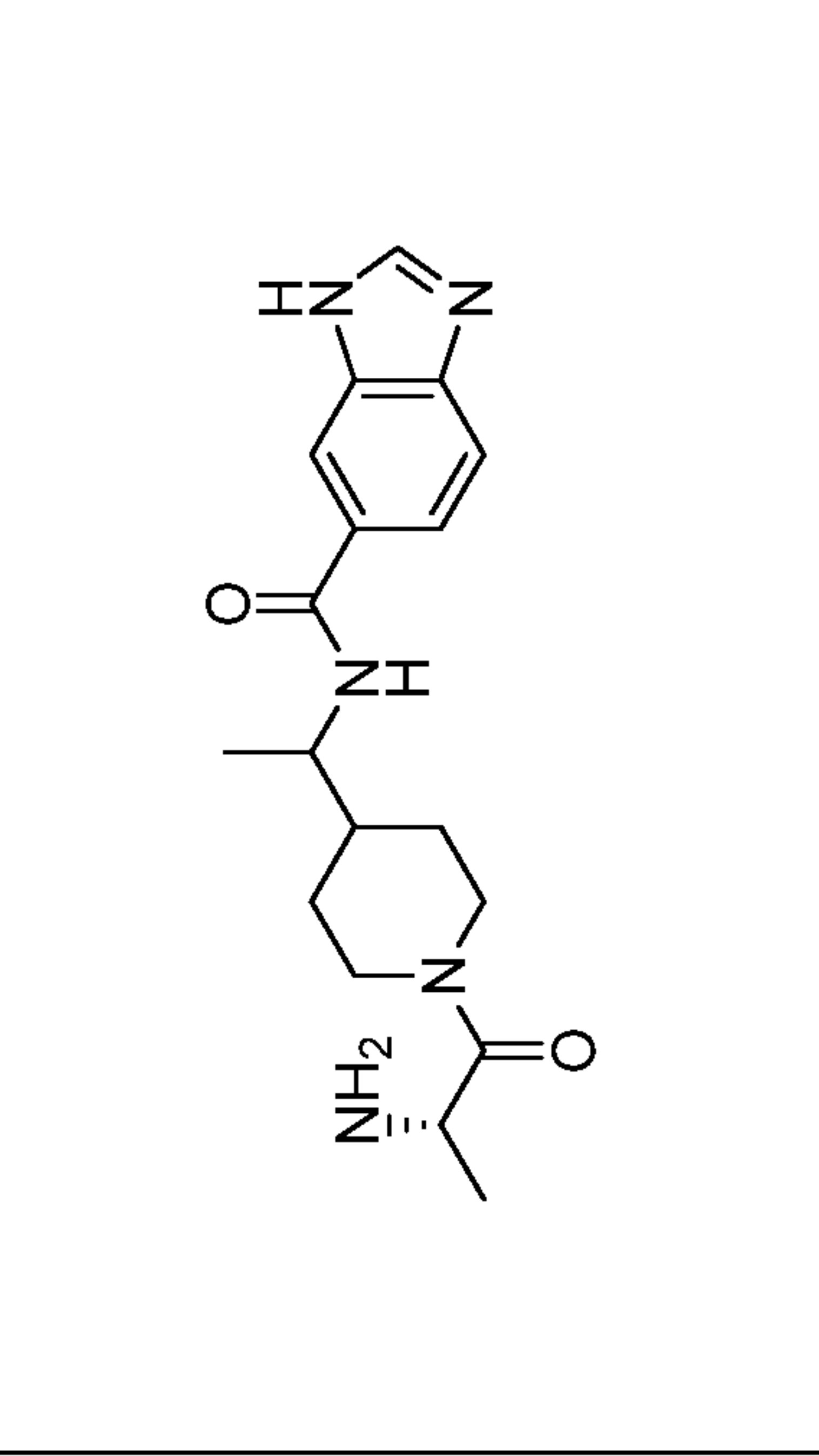
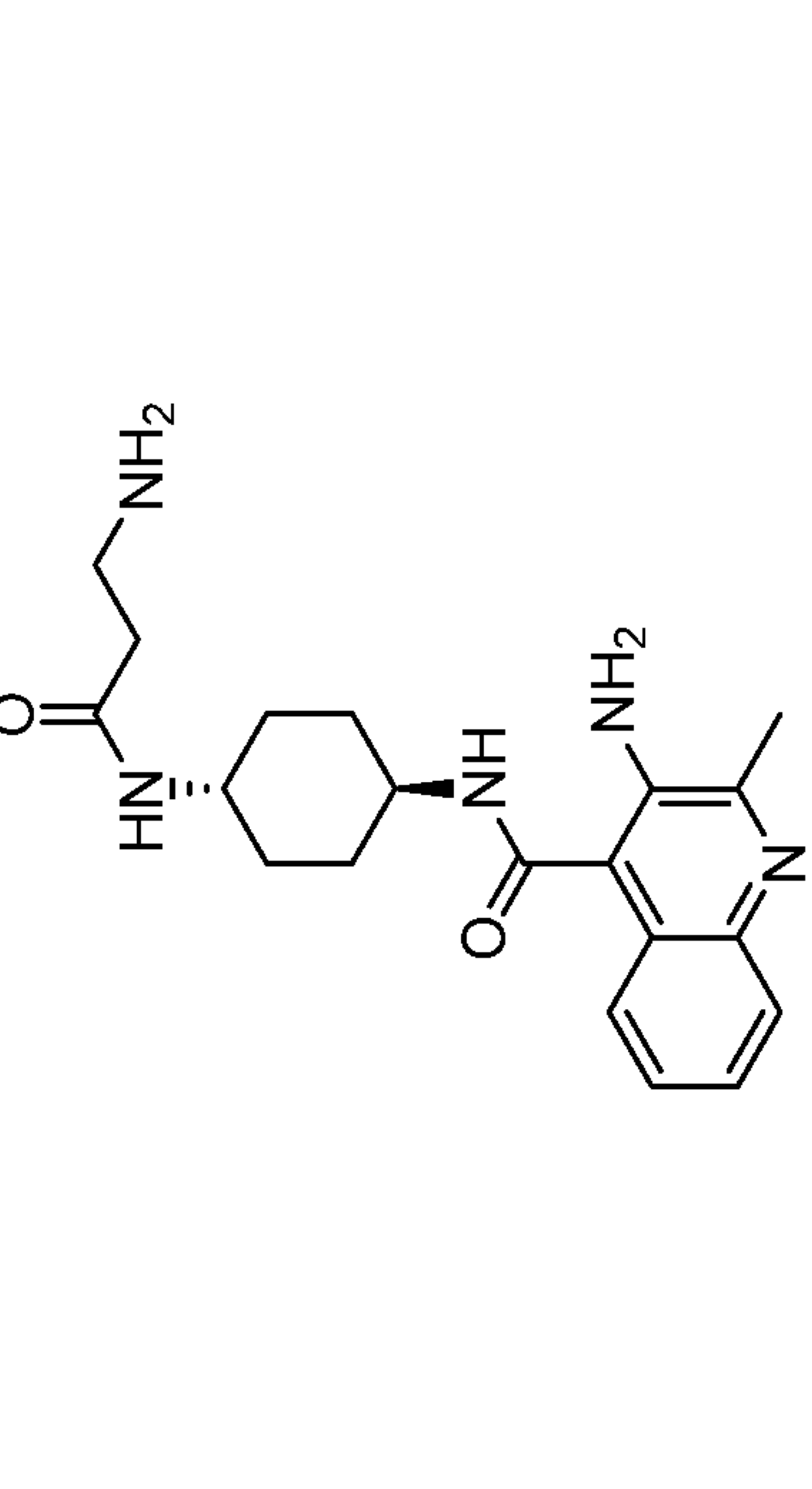
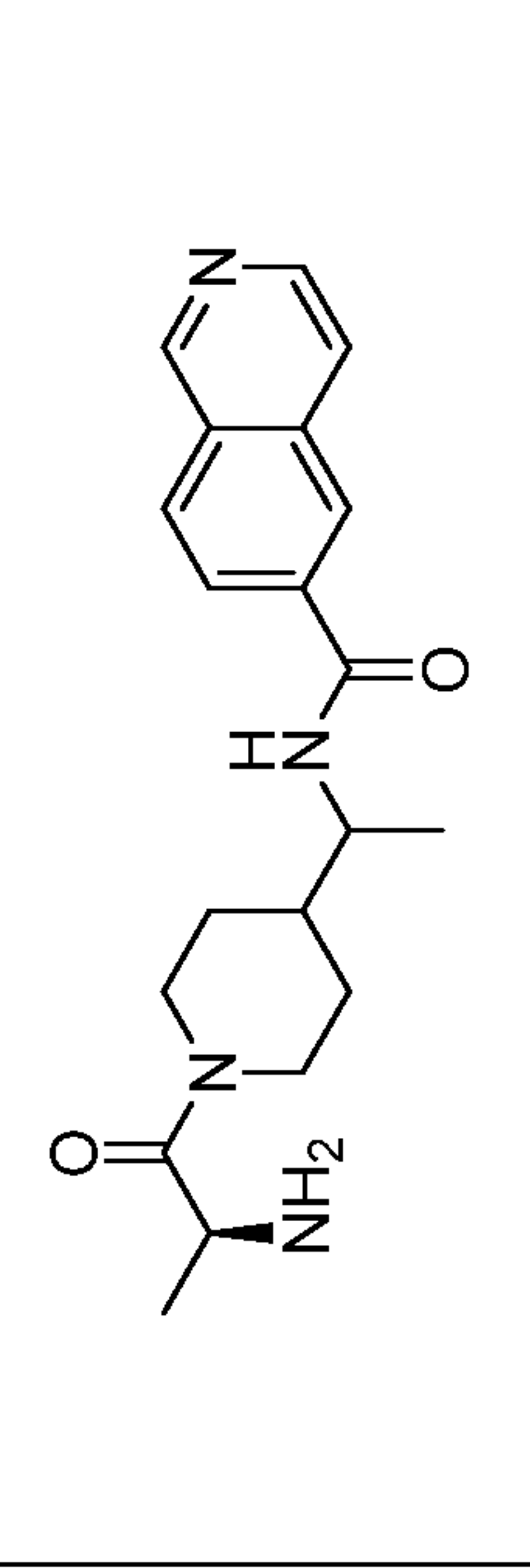
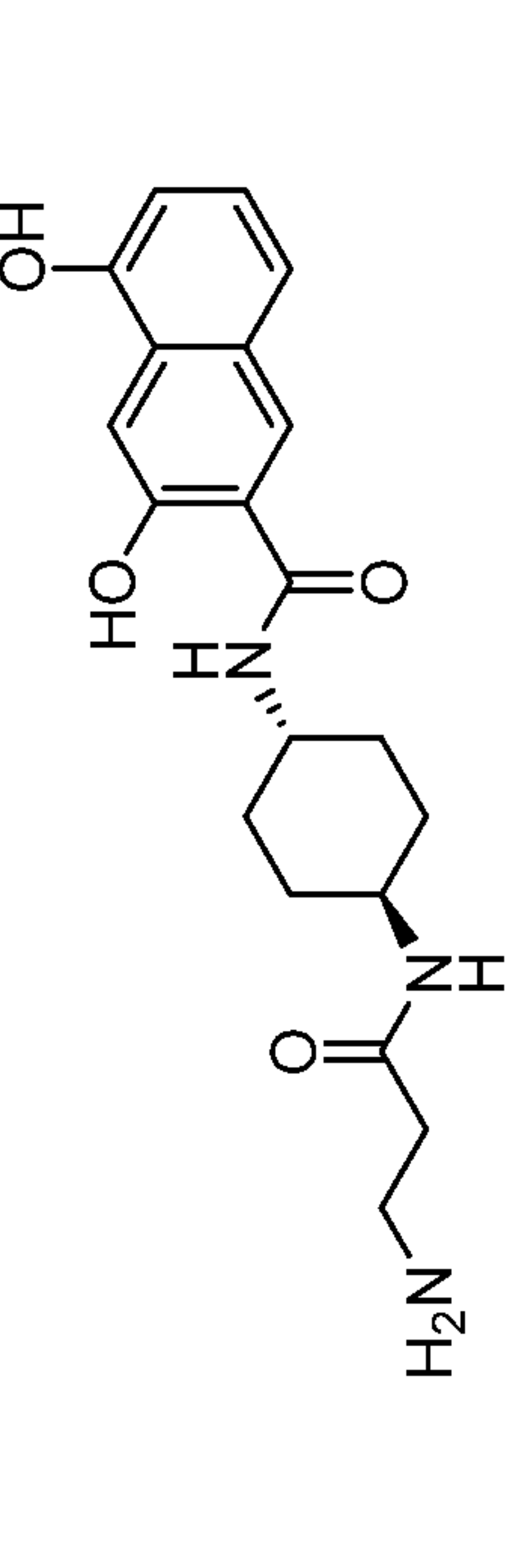
168		HCl	453		TFA
169		TFA	454		TFA
170		TFA	455		None
171		TFA	456		TFA

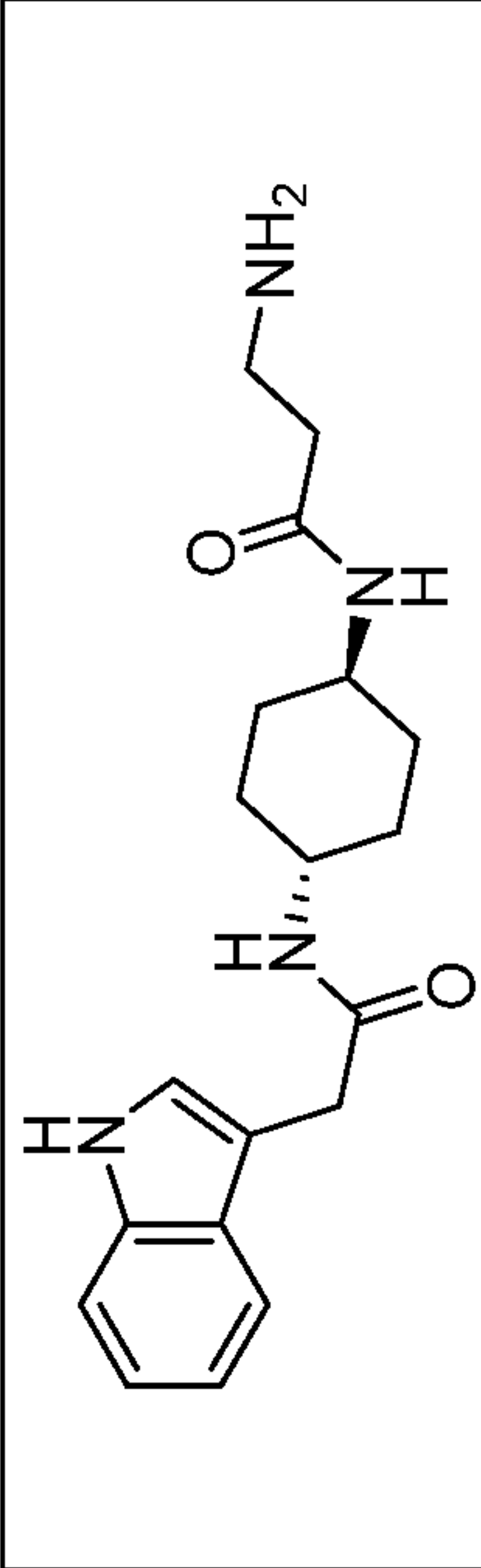
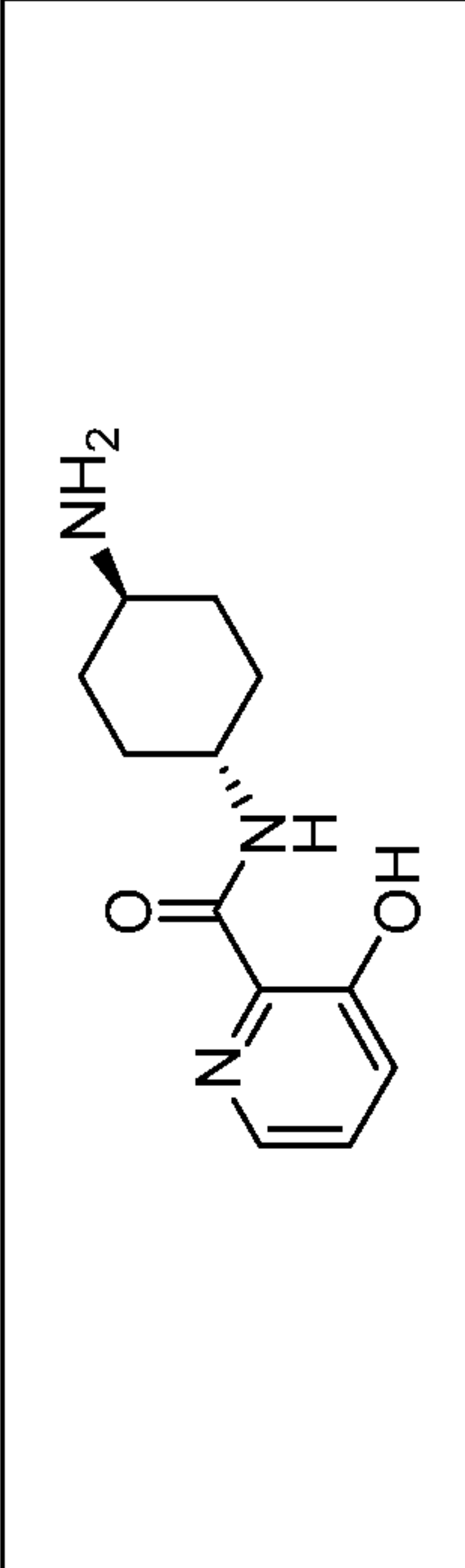
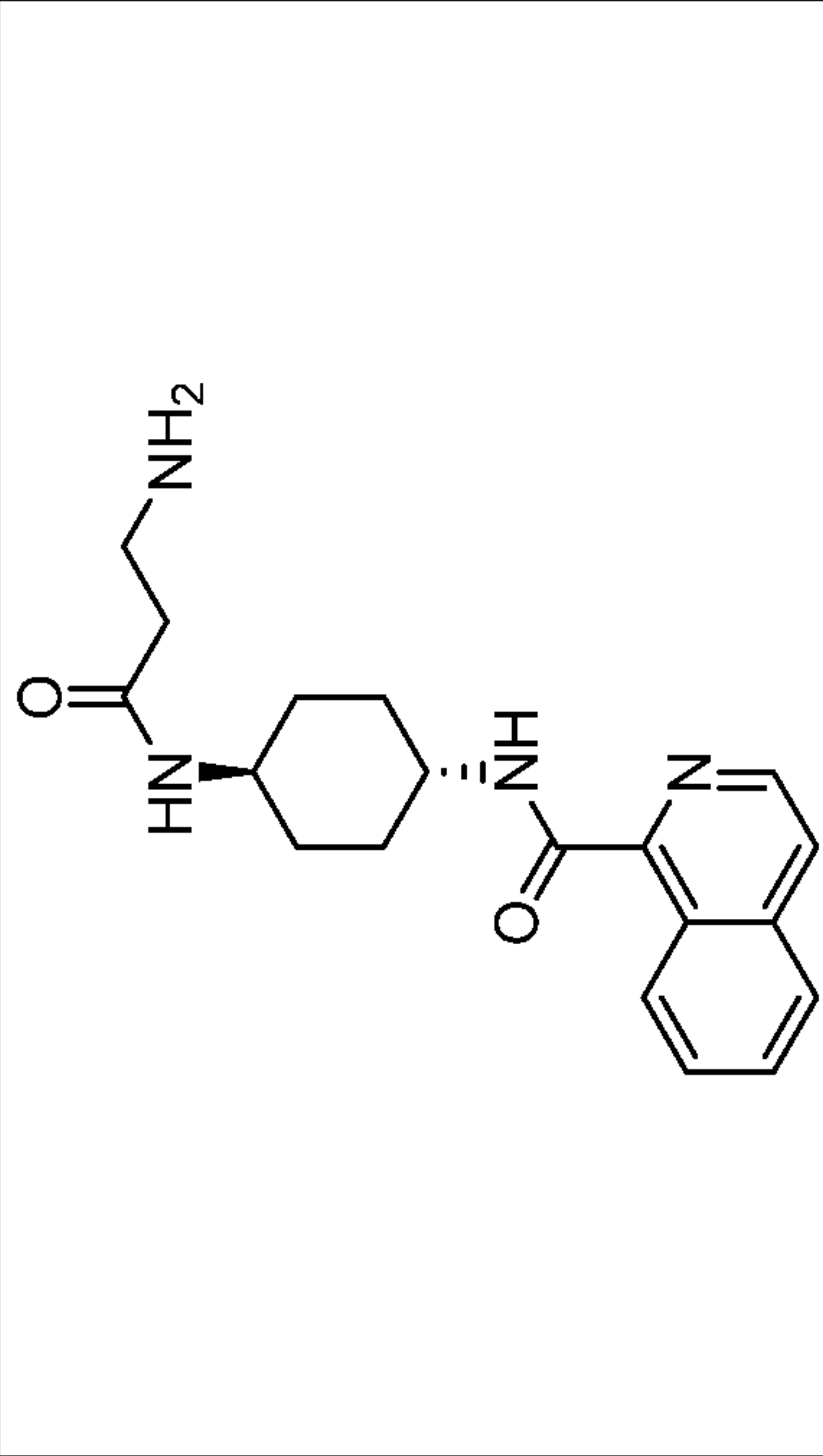
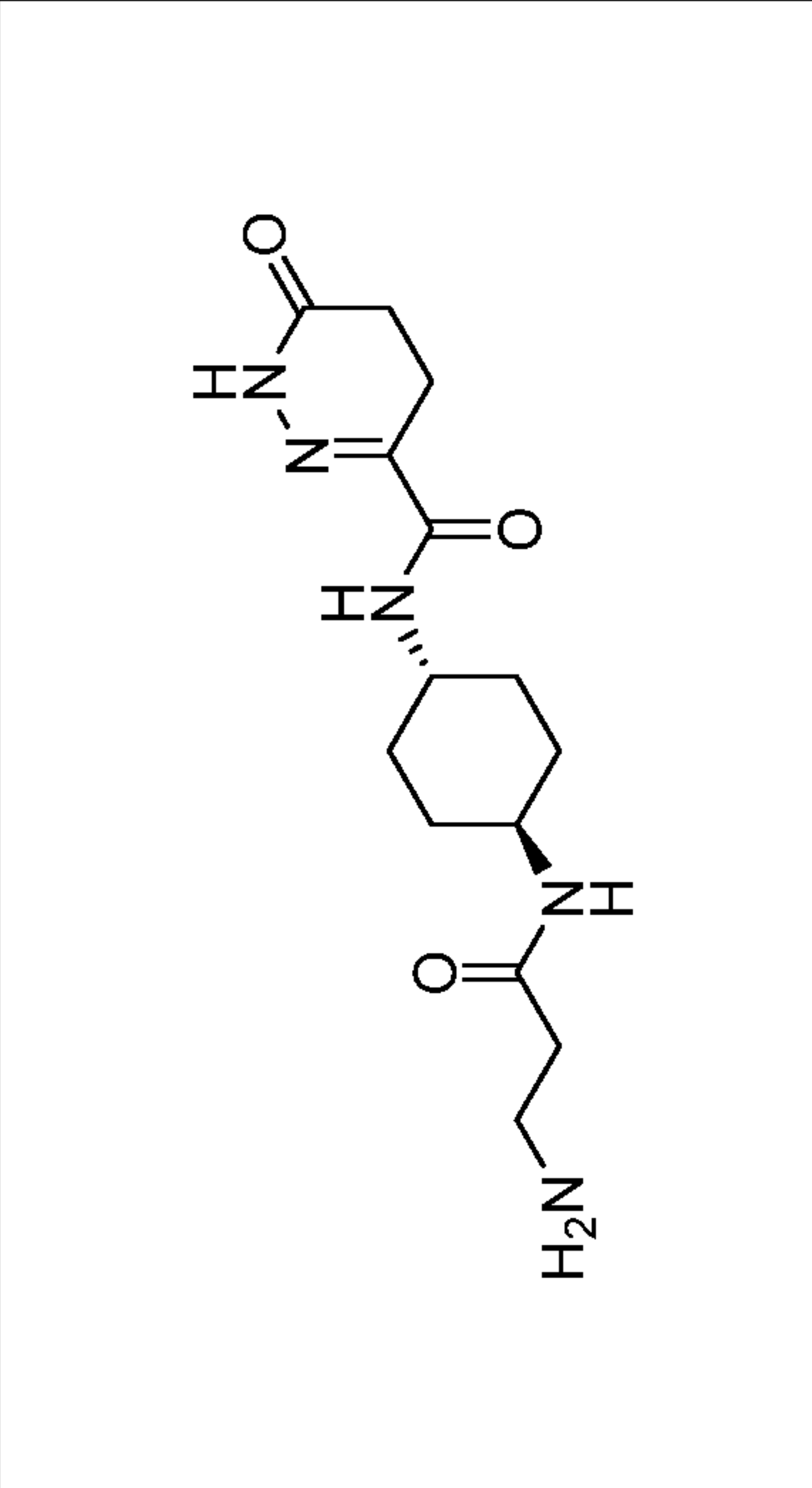
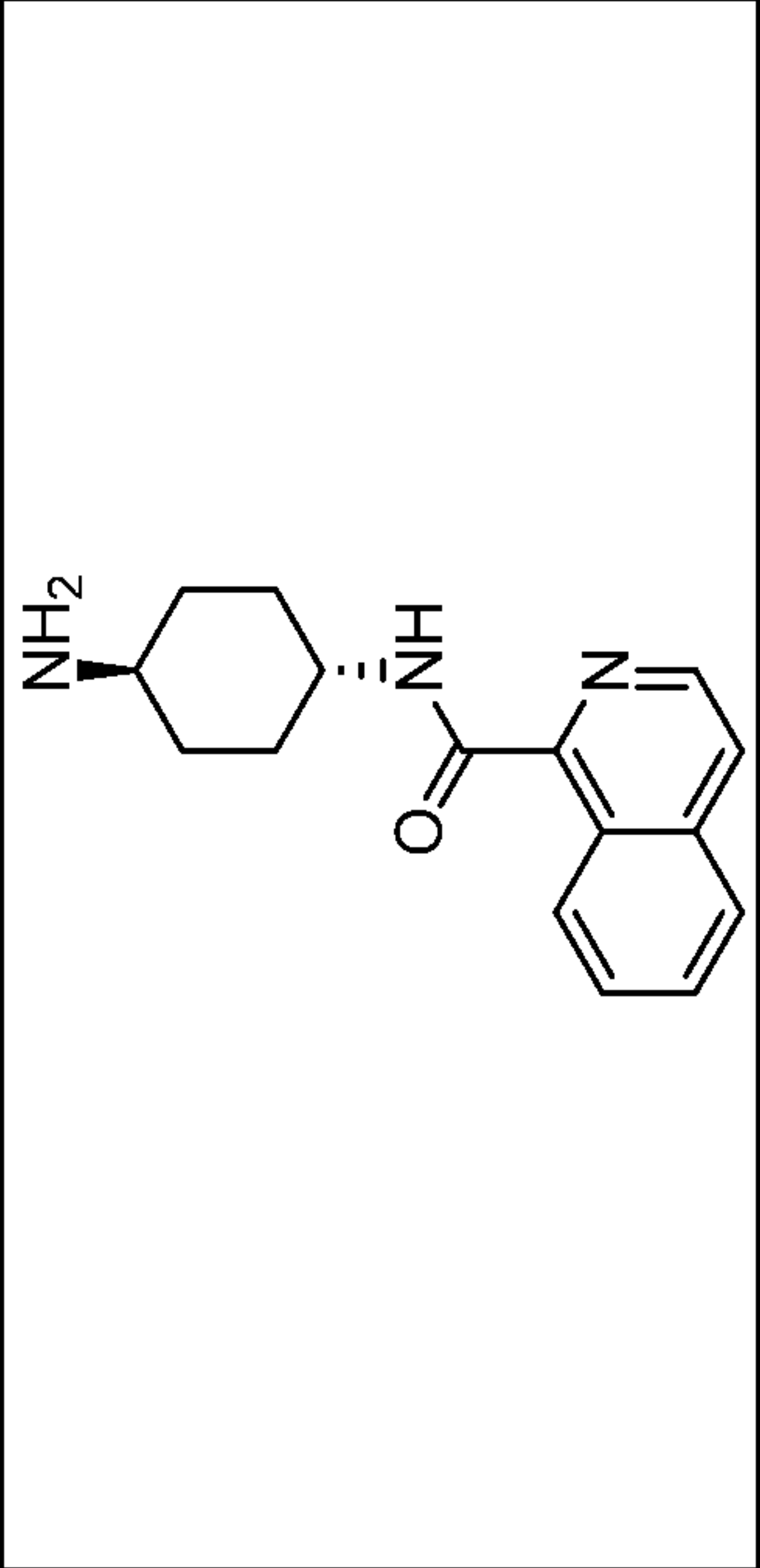
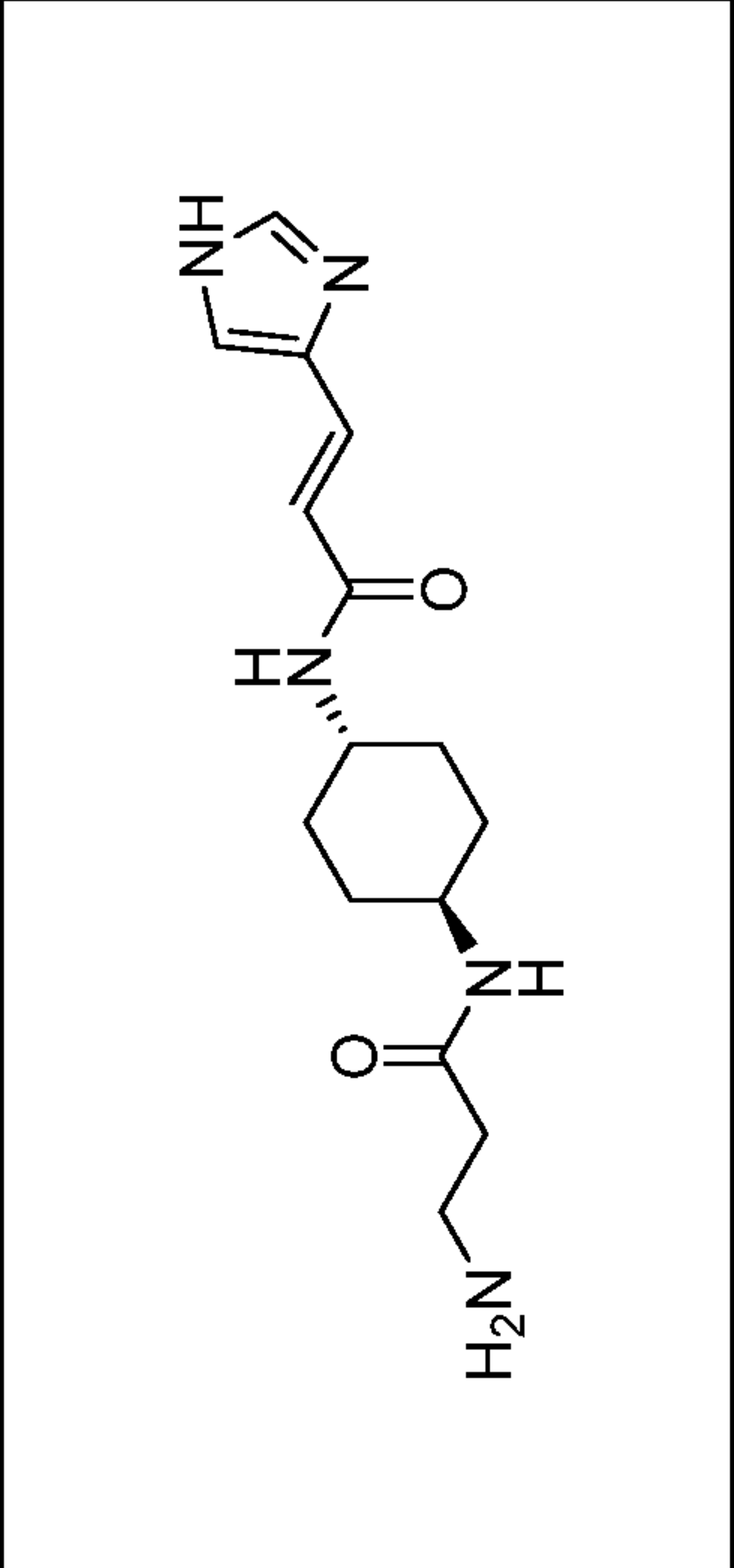
172		TFA	457		TFA
173		TFA	458		None
174		TFA	459		TFA
175		TFA	460		TFA

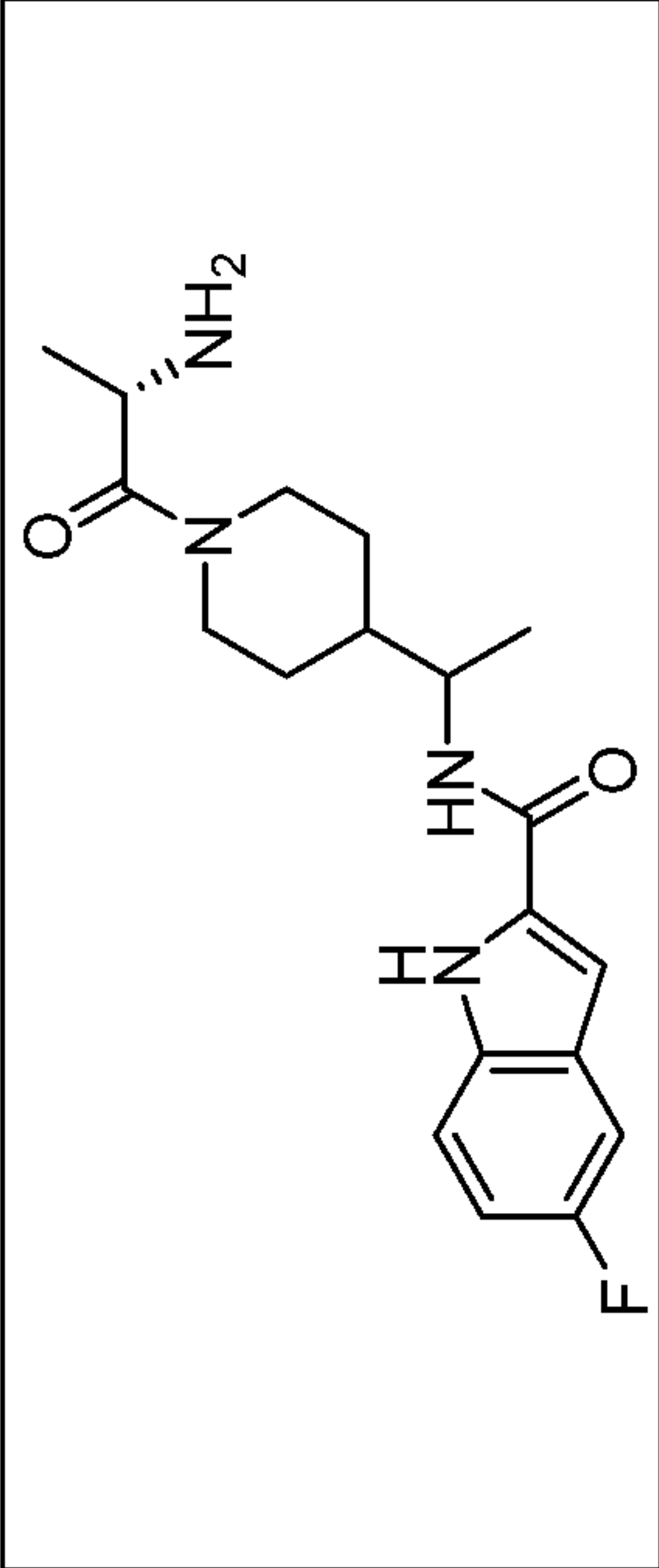
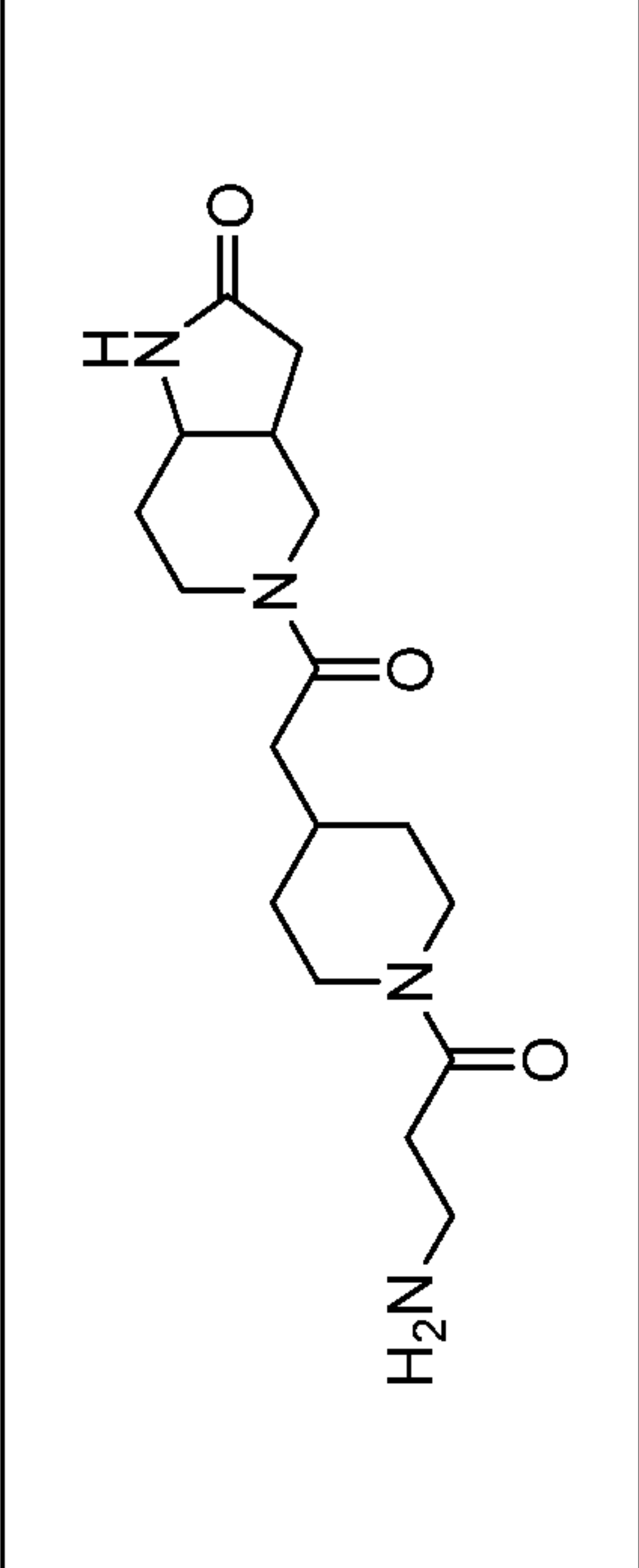
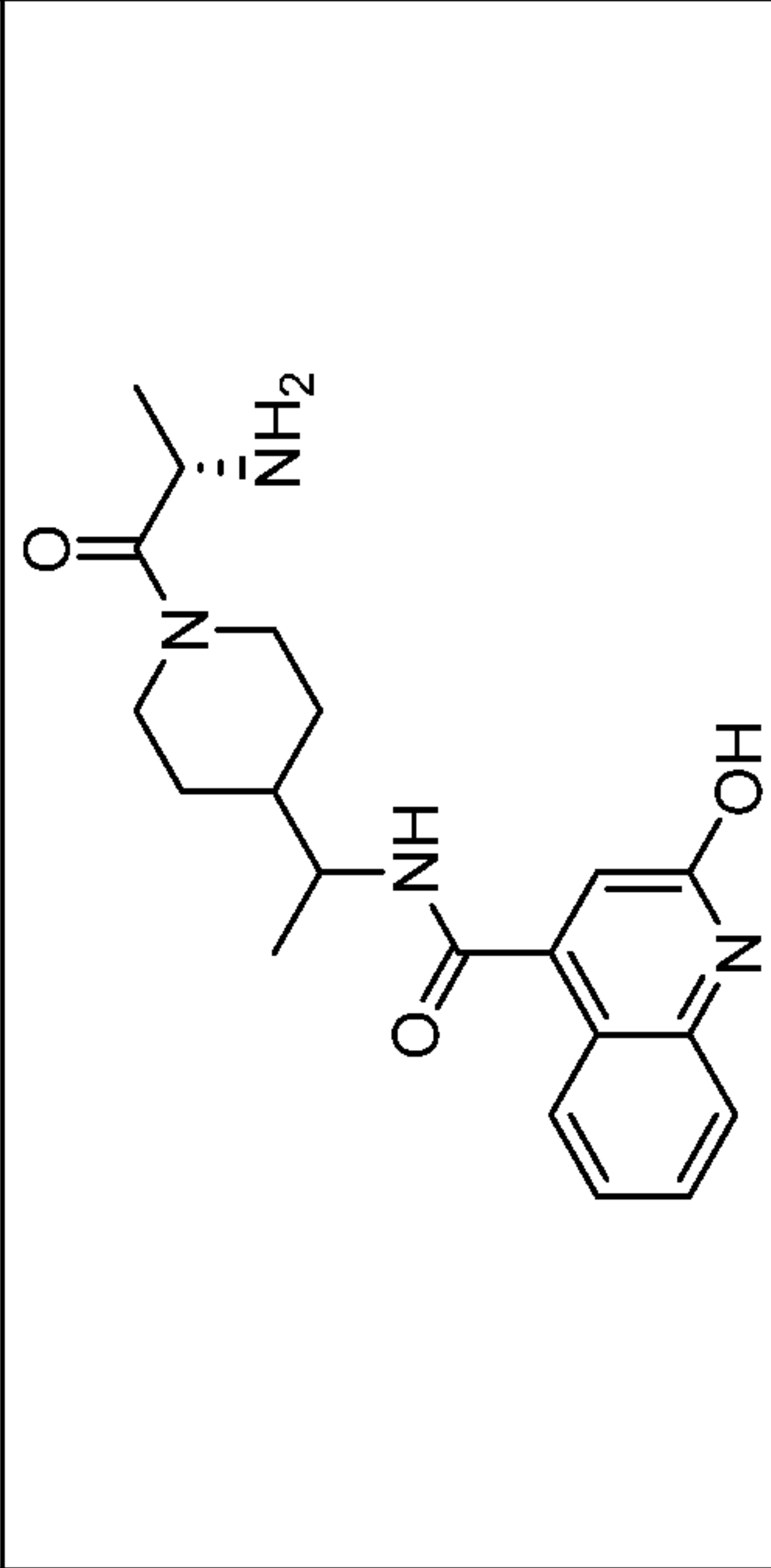
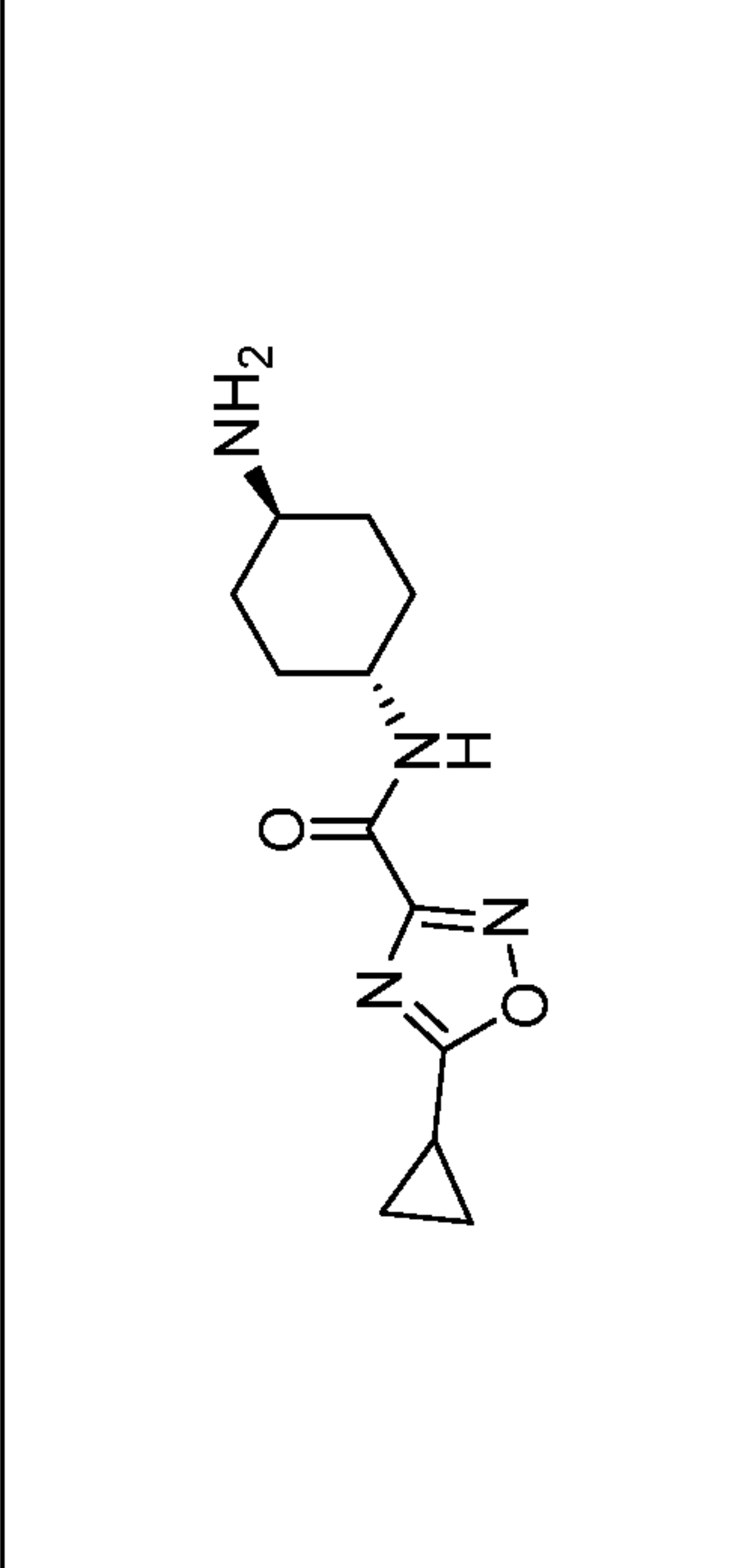
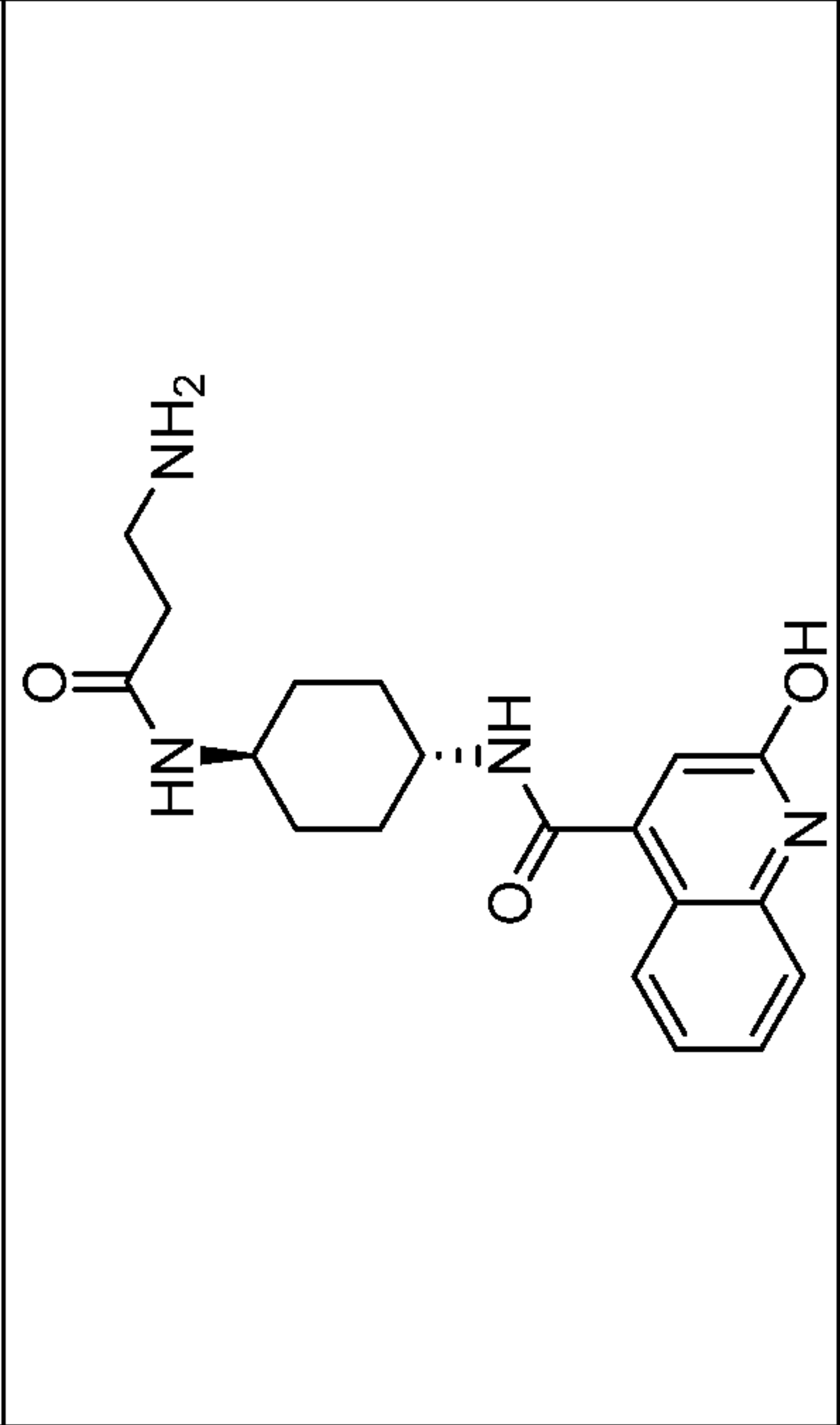
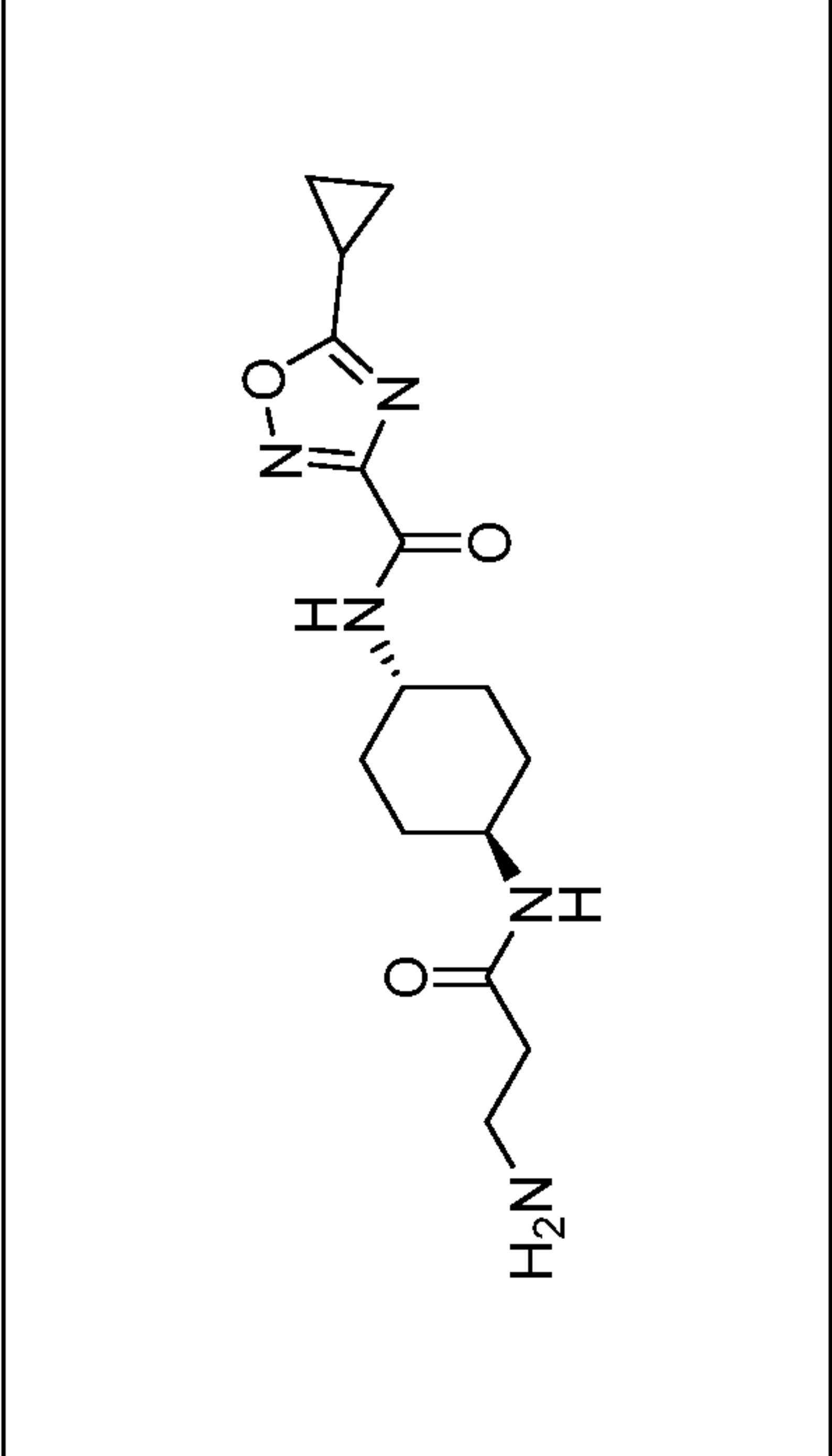
176		HCO OH	461		TFA
177		TFA	462		TFA
178		TFA	463		TFA
179		HCl	464		HCl
180		HCl	465		TFA

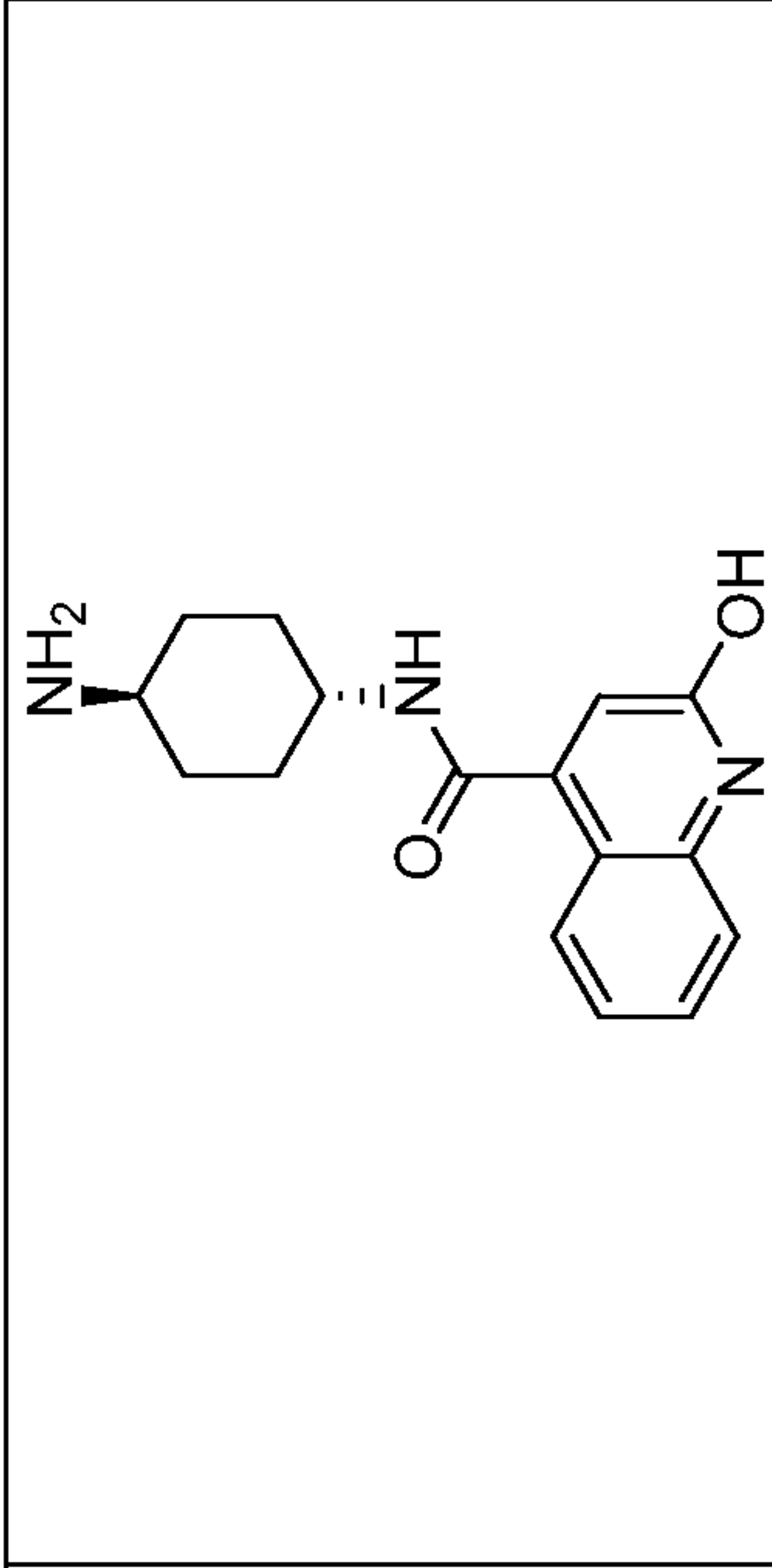
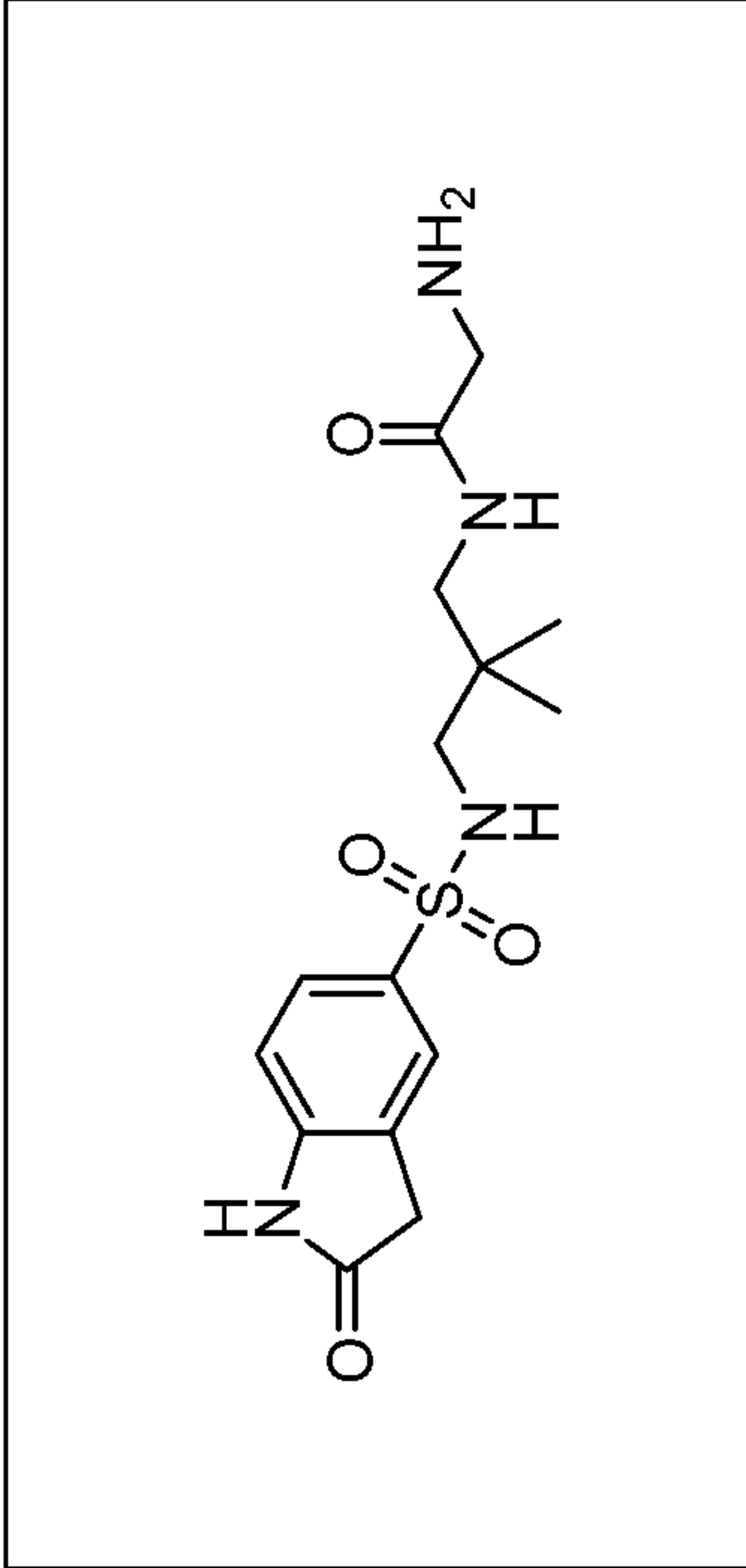
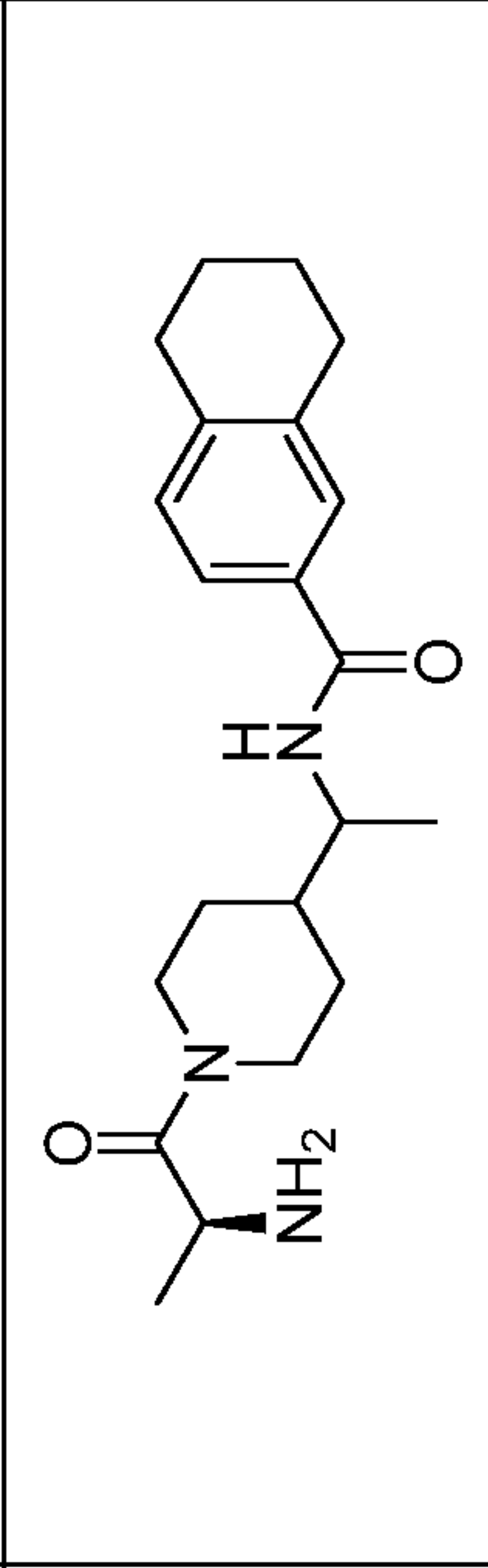
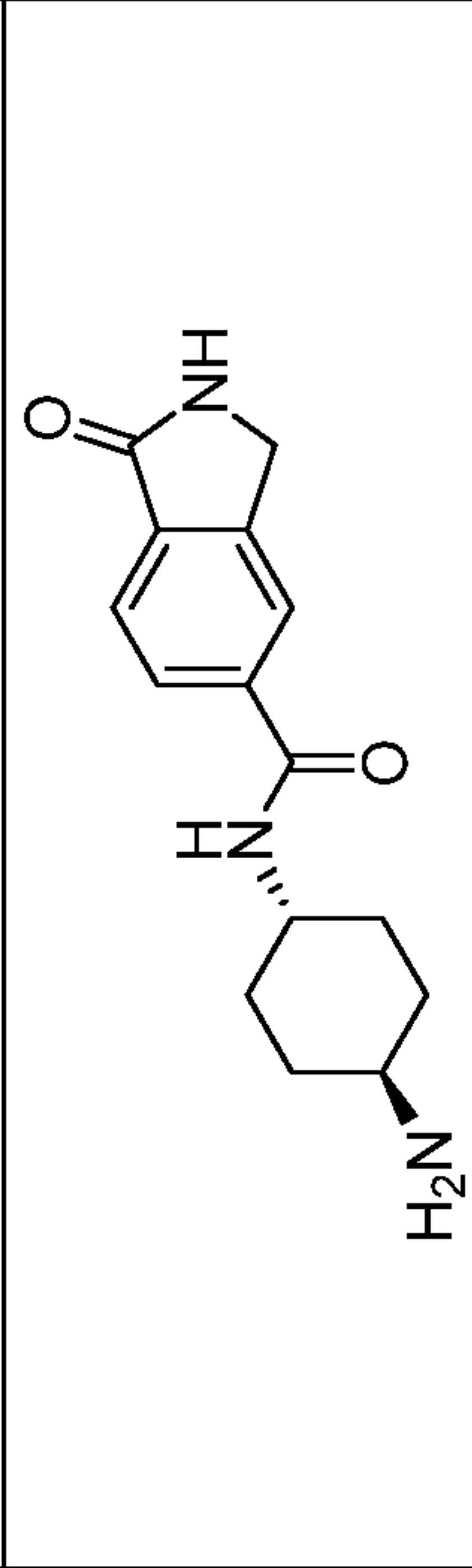
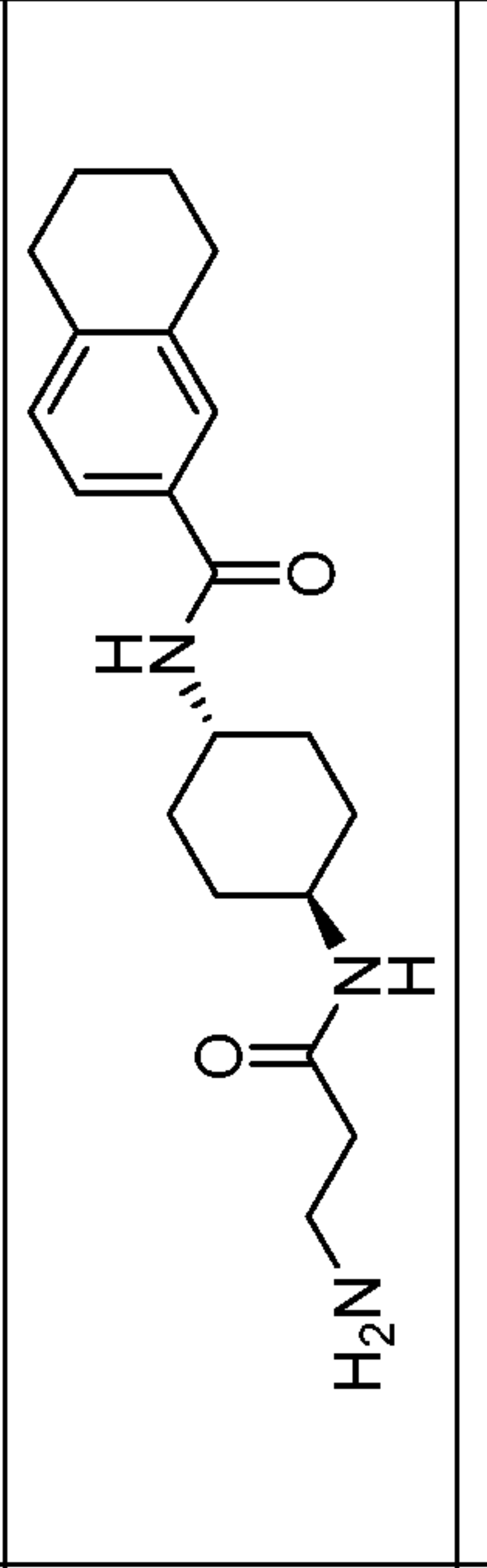
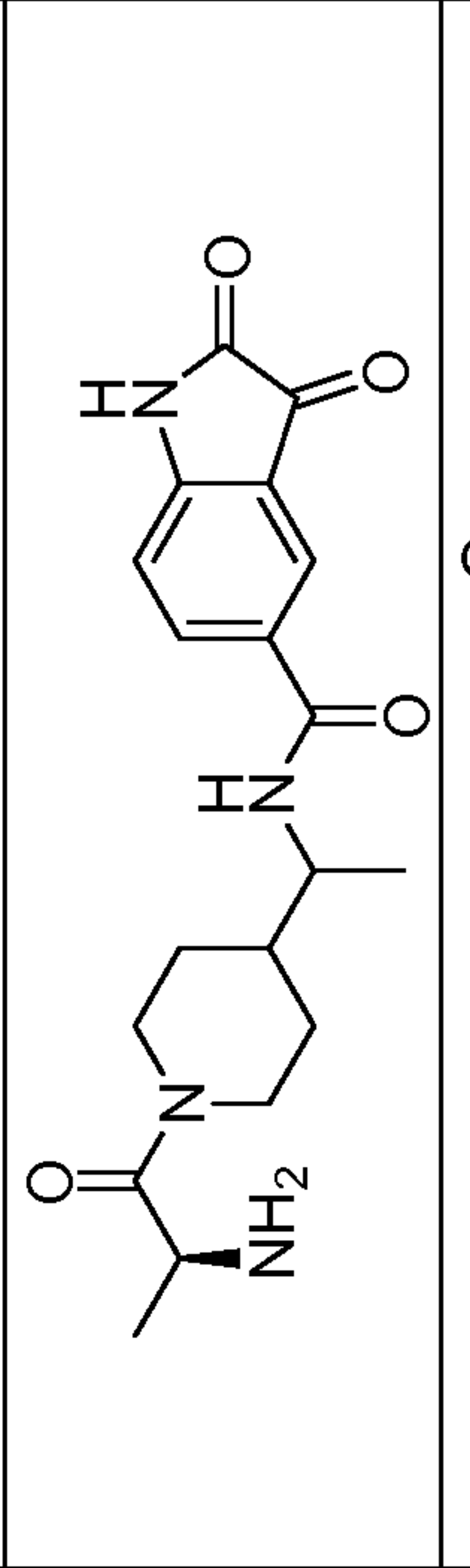
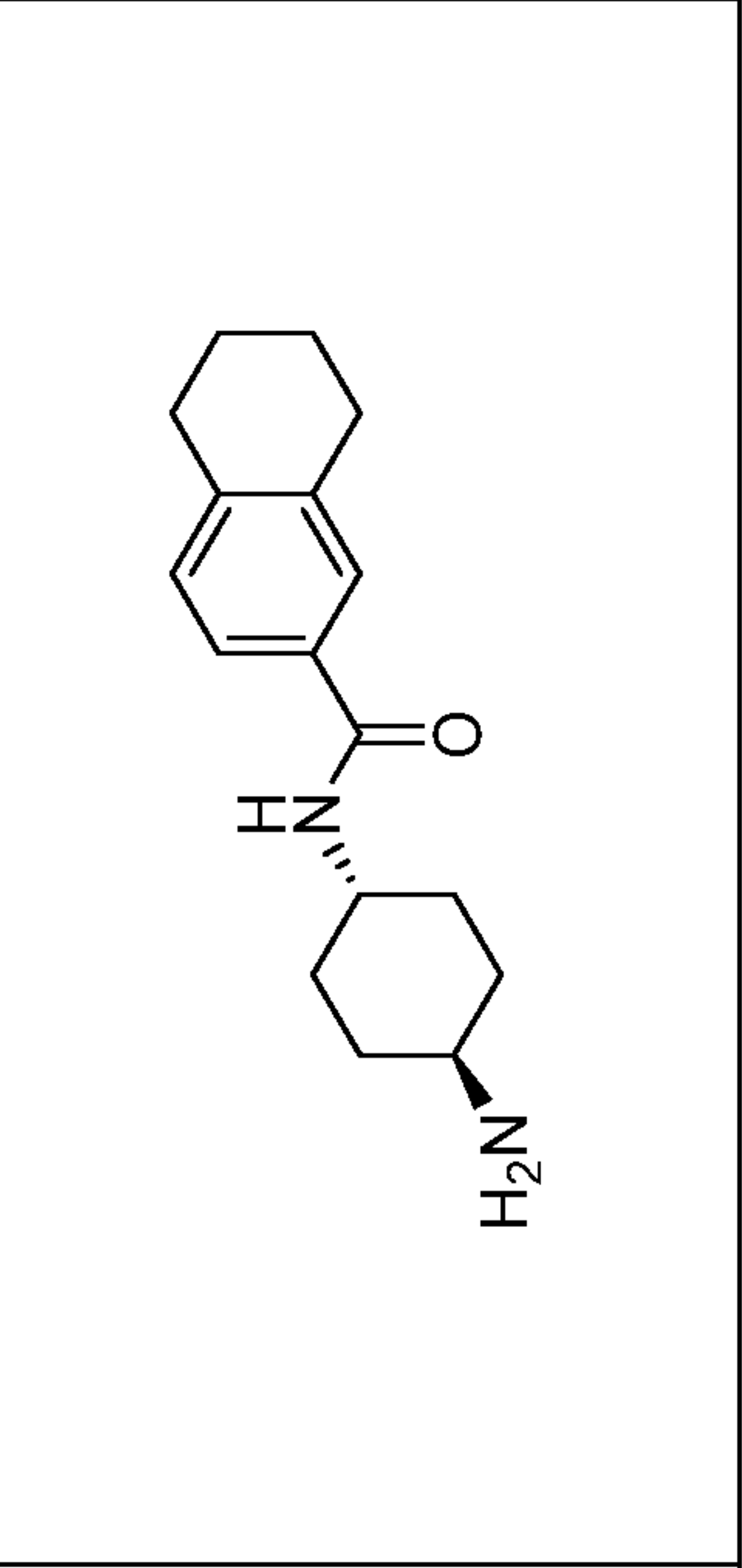
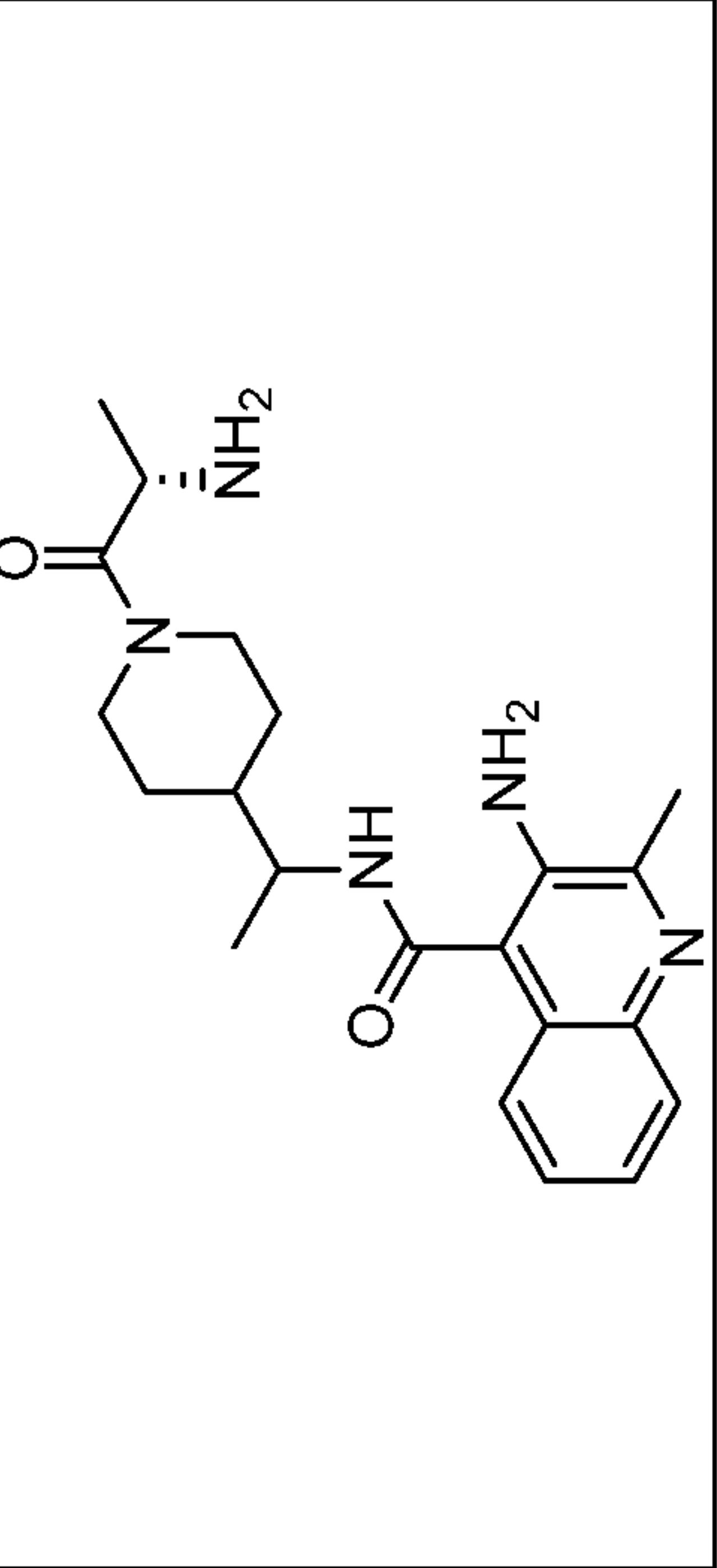
181		None	466		TFA
182		None	467		TFA
183		None	468		TFA
184		HCl	469		TFA
185		TFA	470		TFA

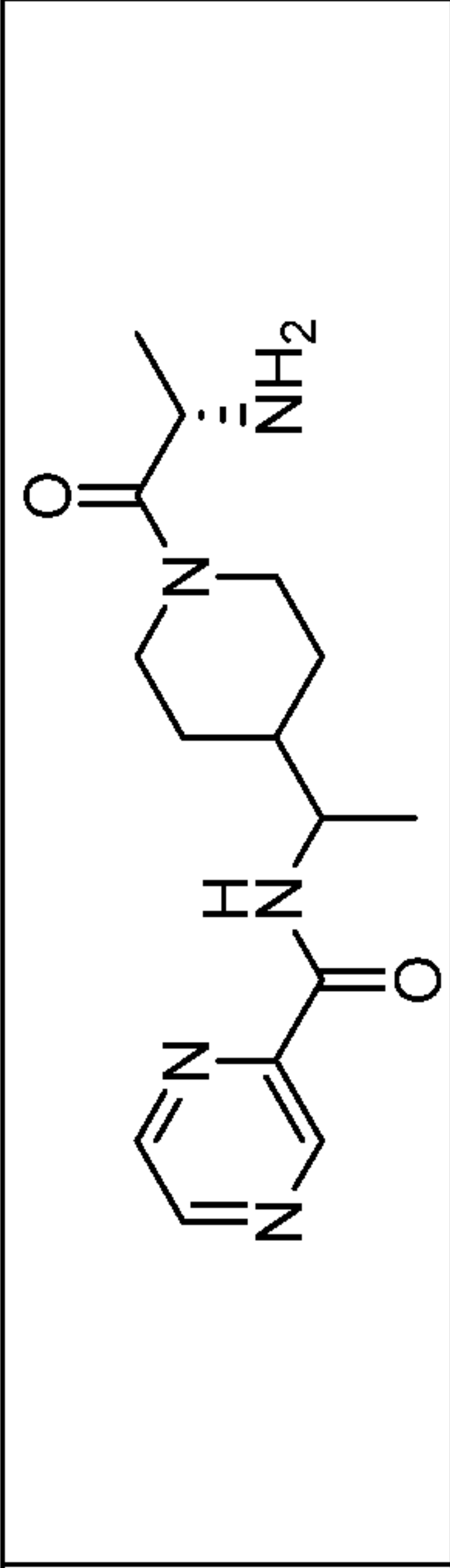
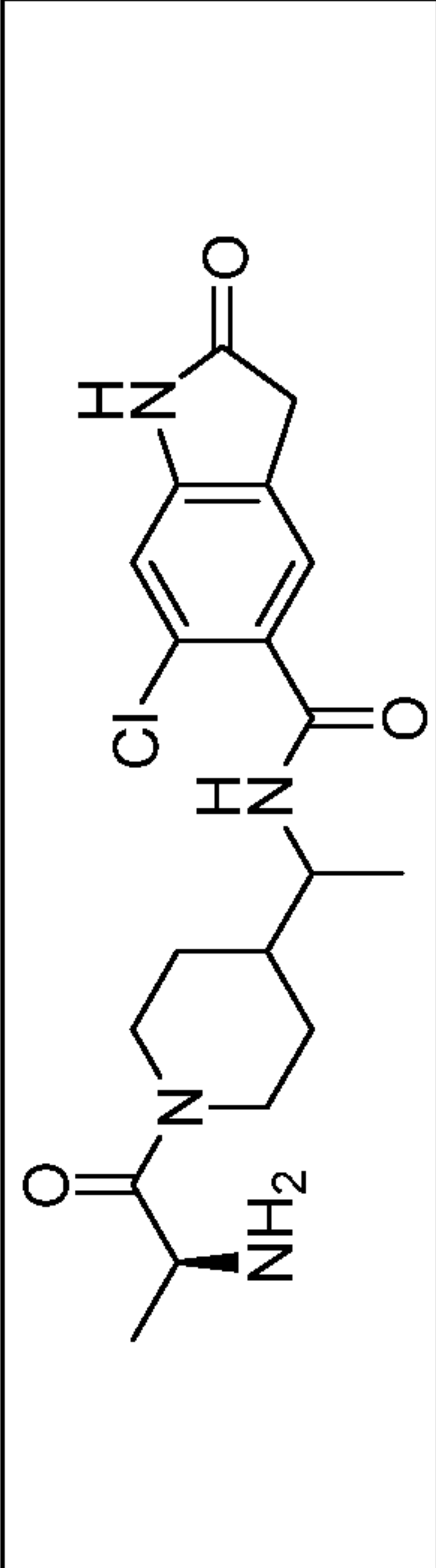
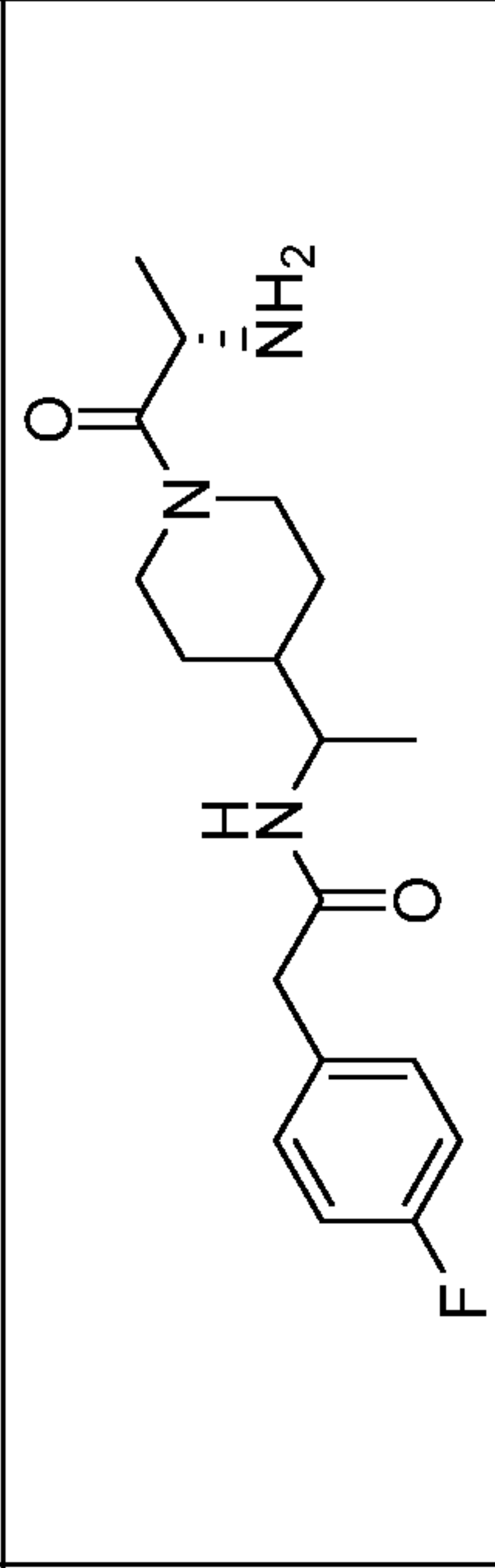
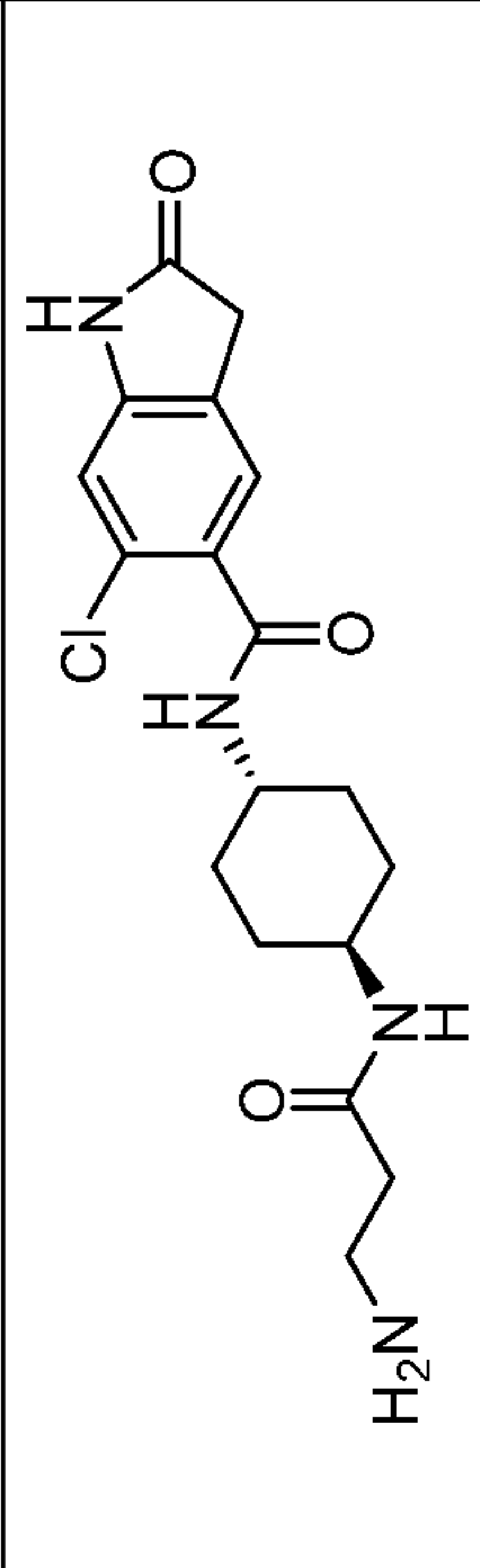
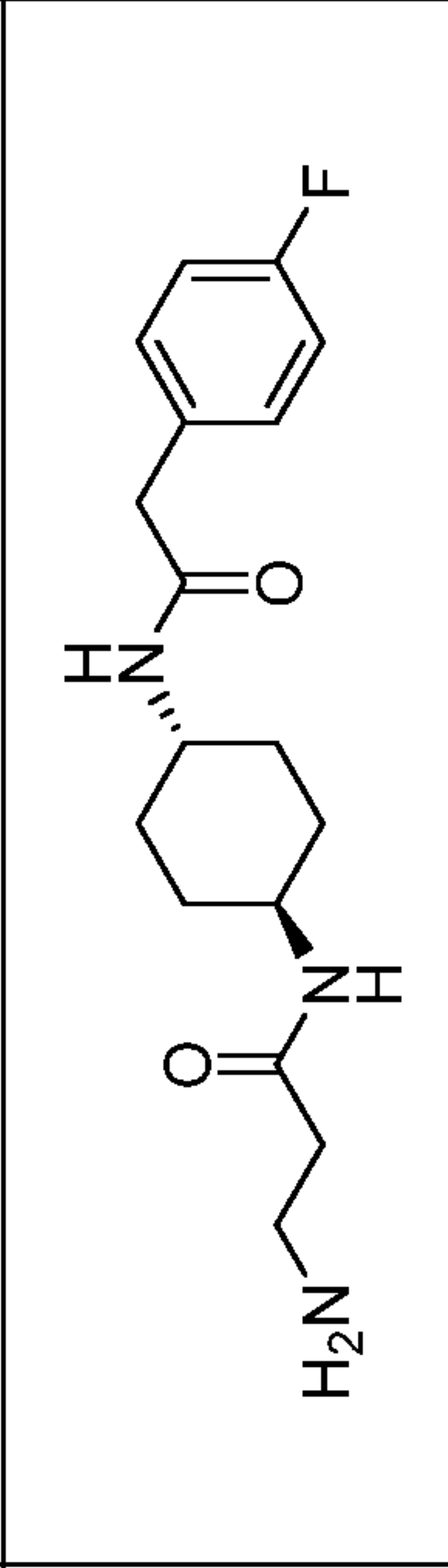
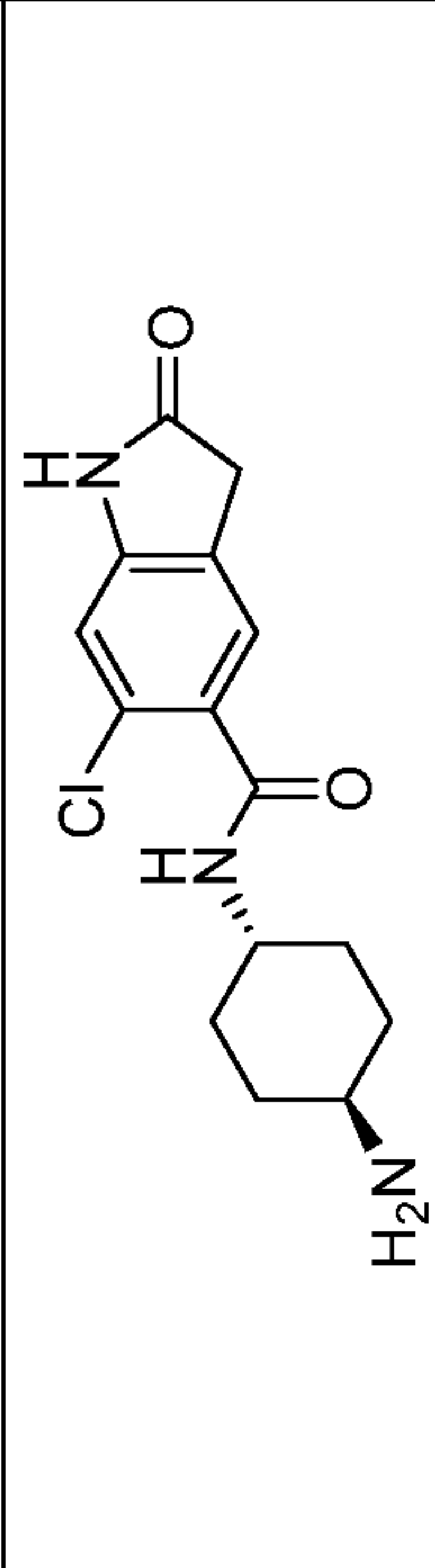
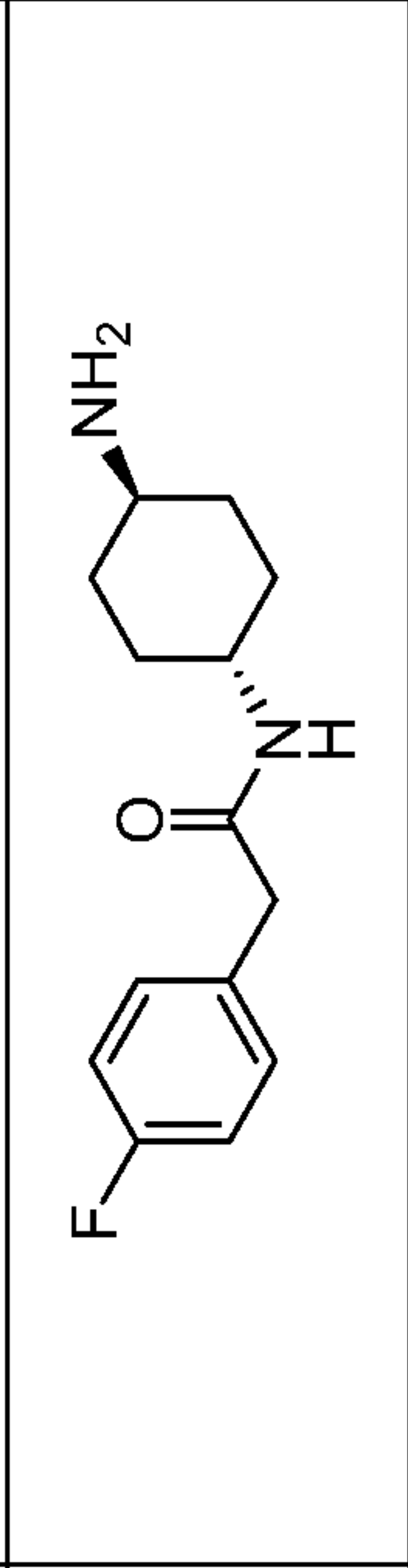
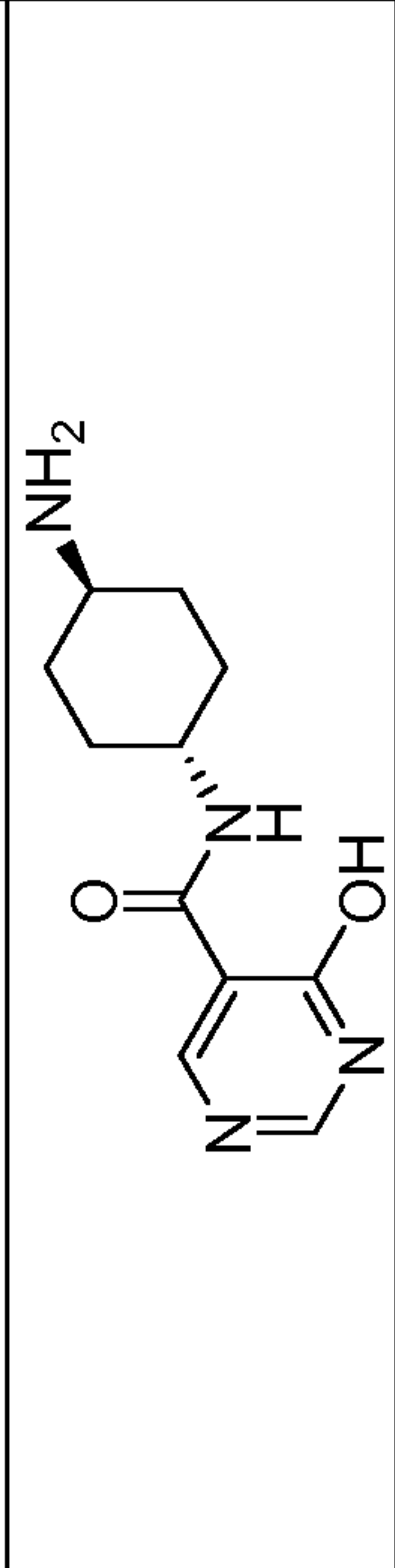
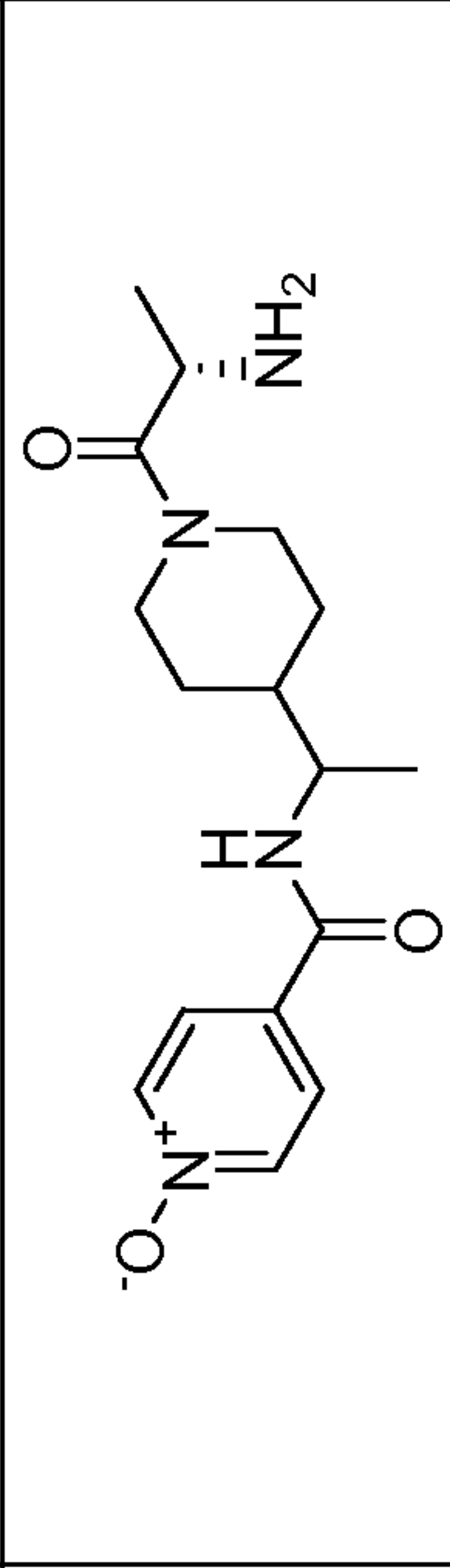
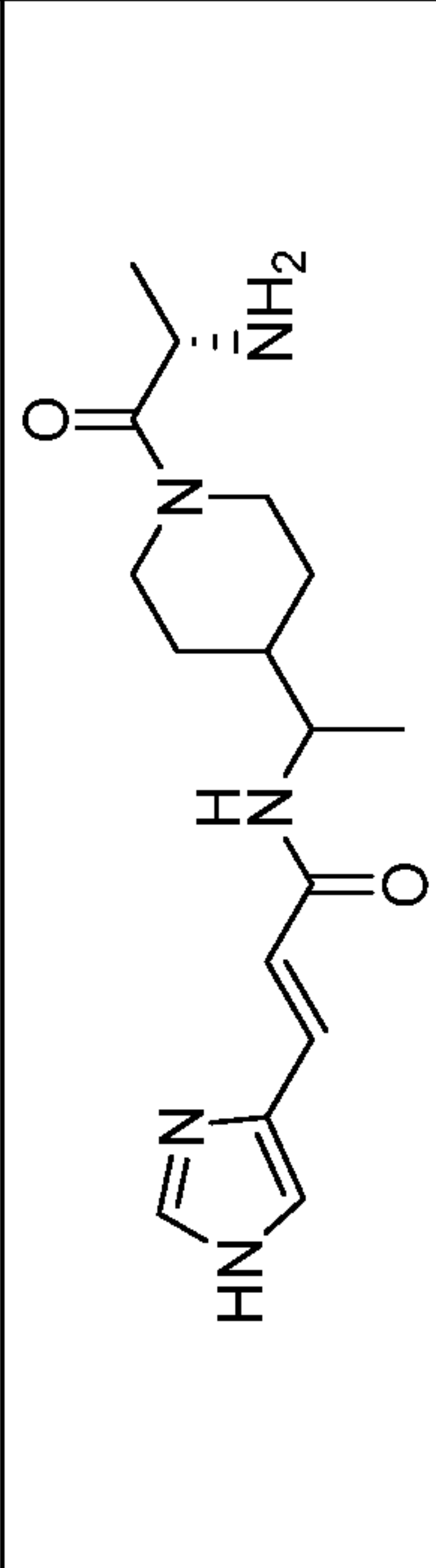
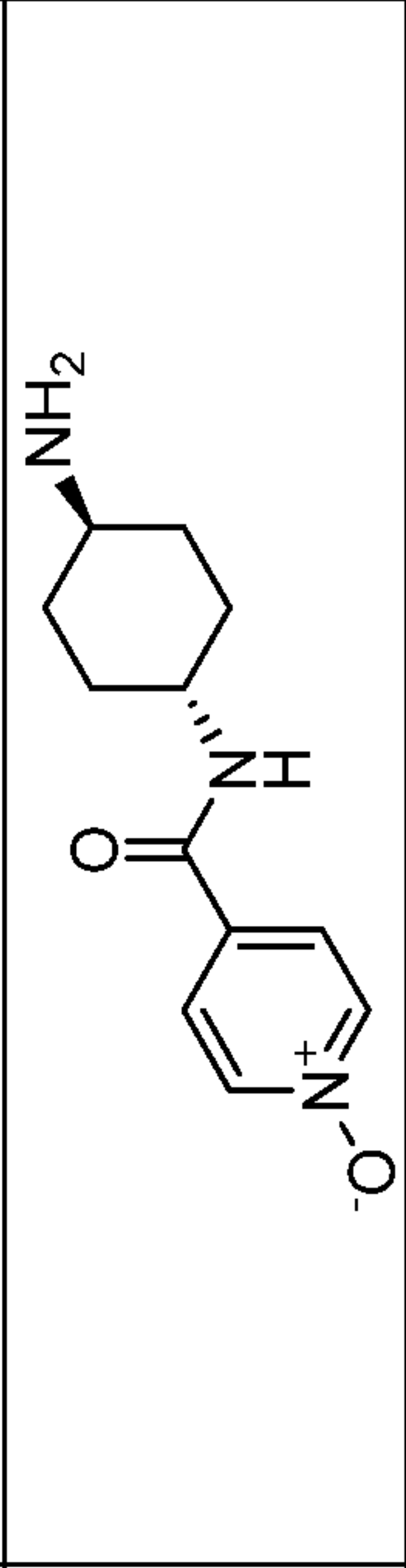
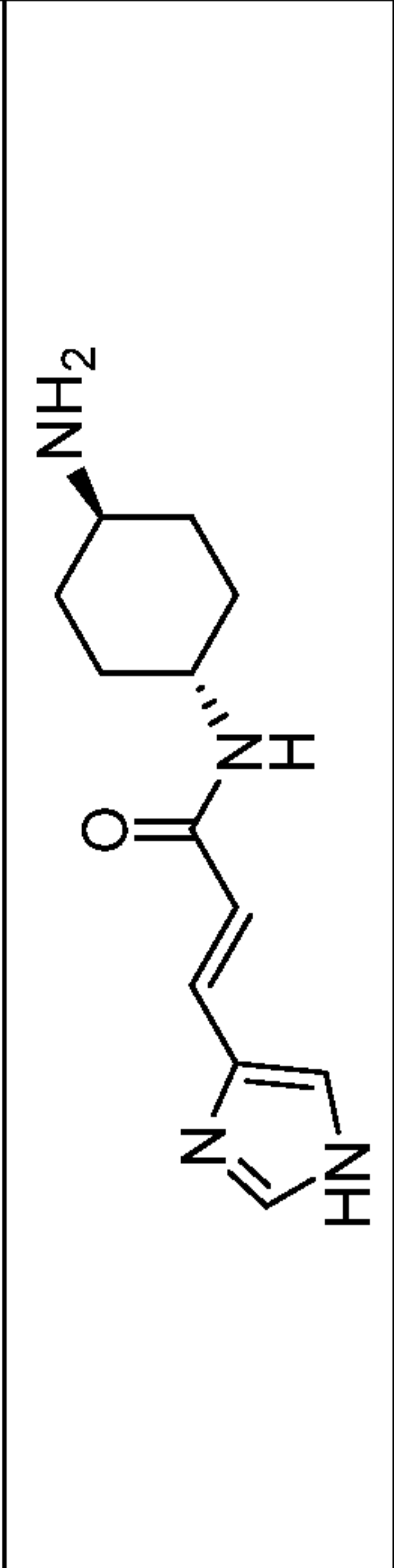
186		TFA	471		HCl
187		HCl	472		None
188		HCl	473		TFA
189		HCl	474		TFA
190		HCl	475		TFA

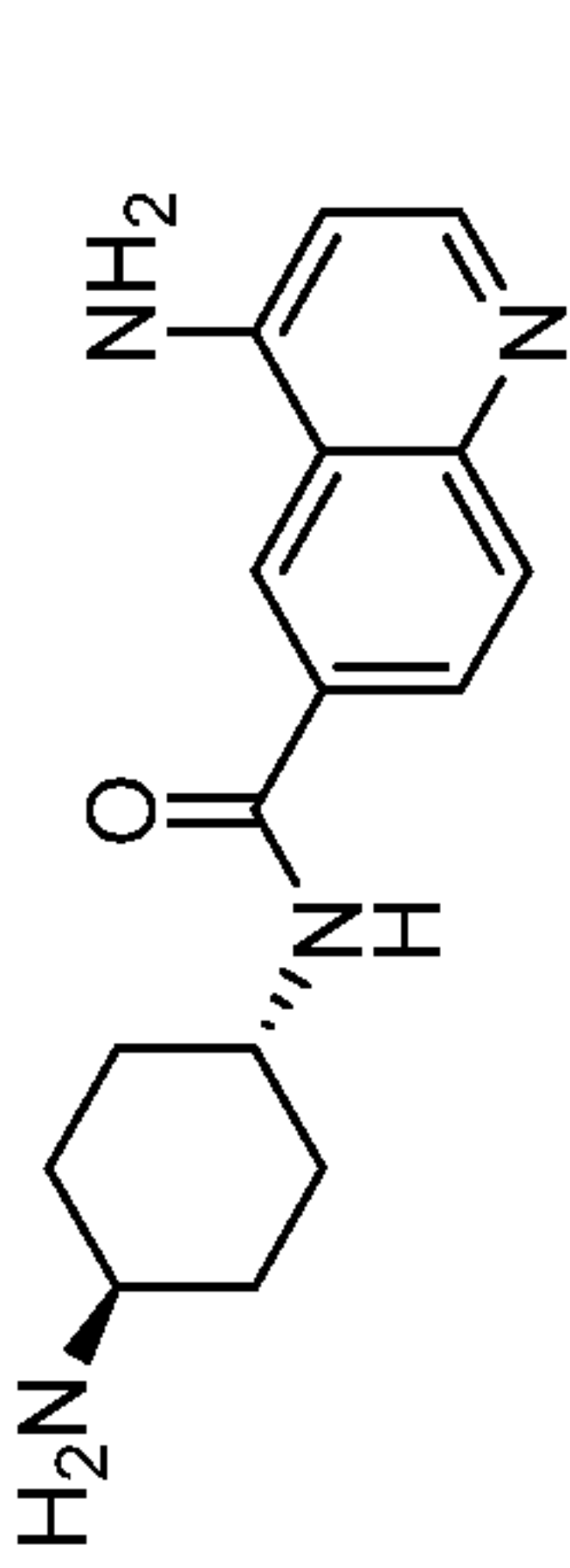
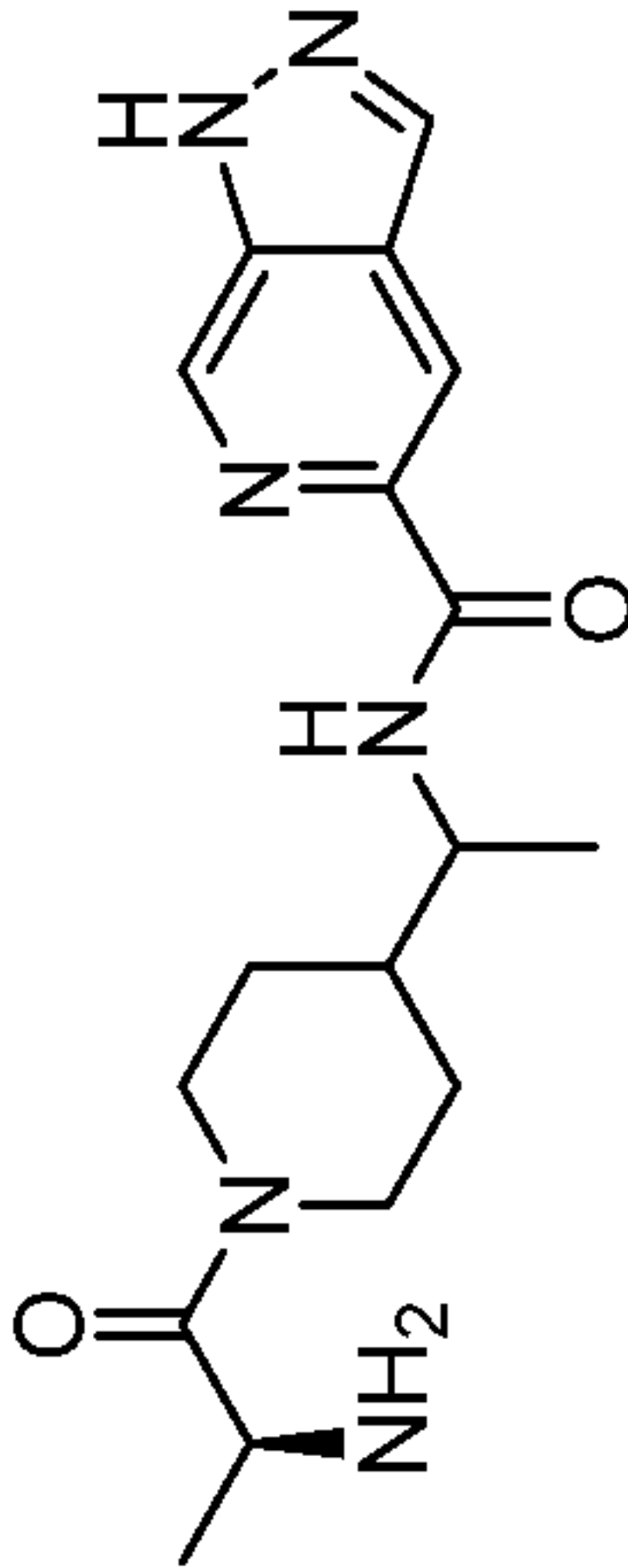
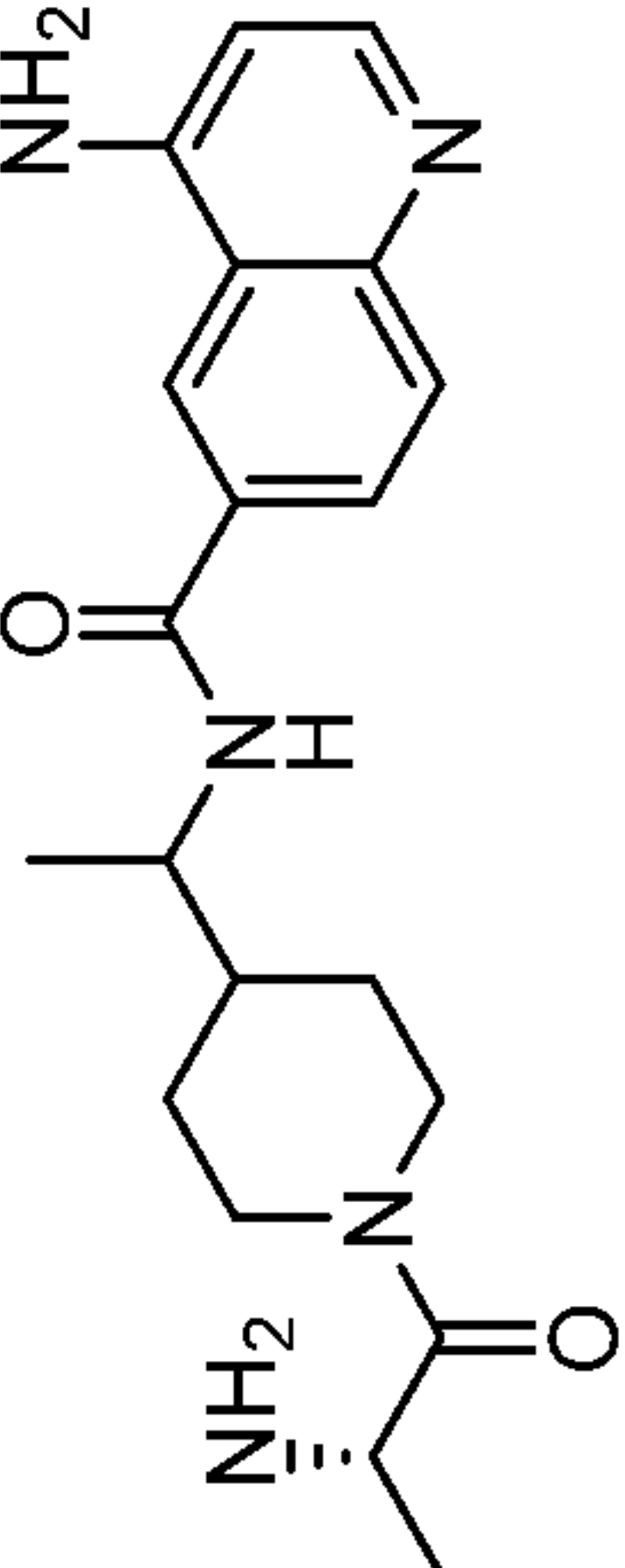
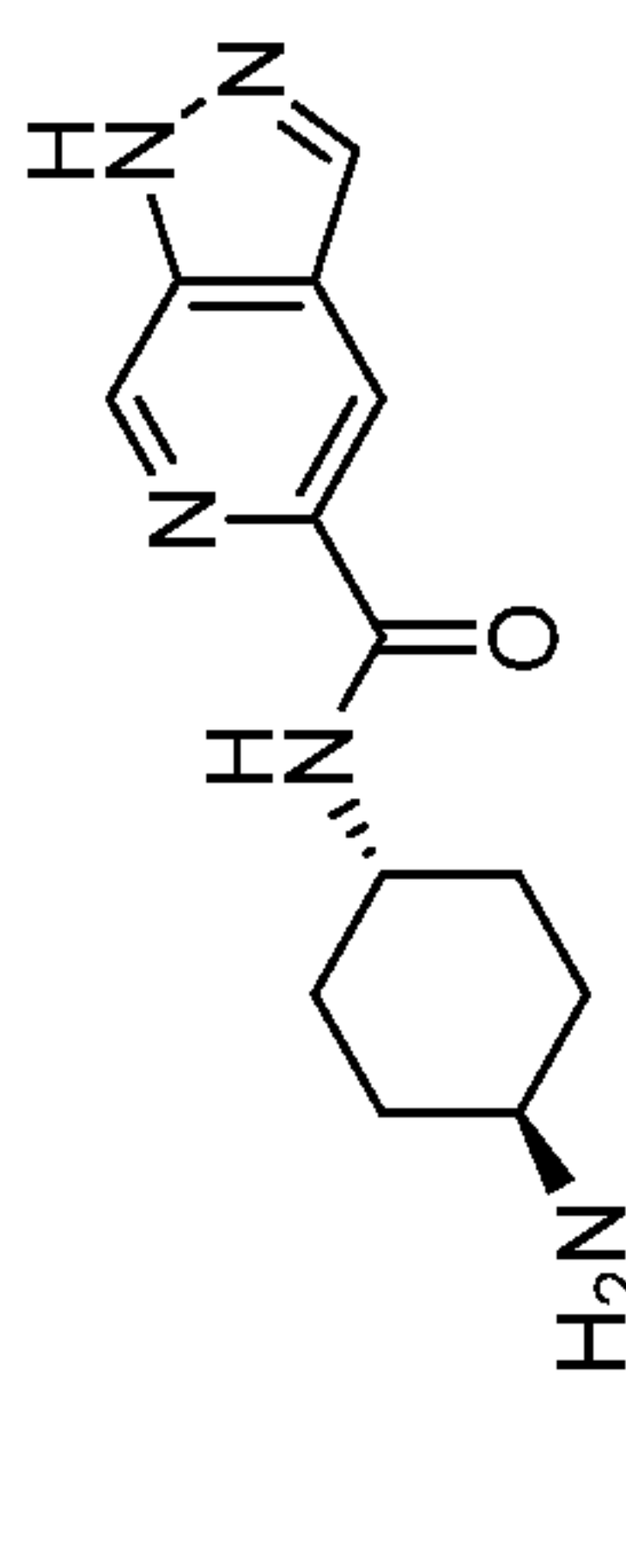
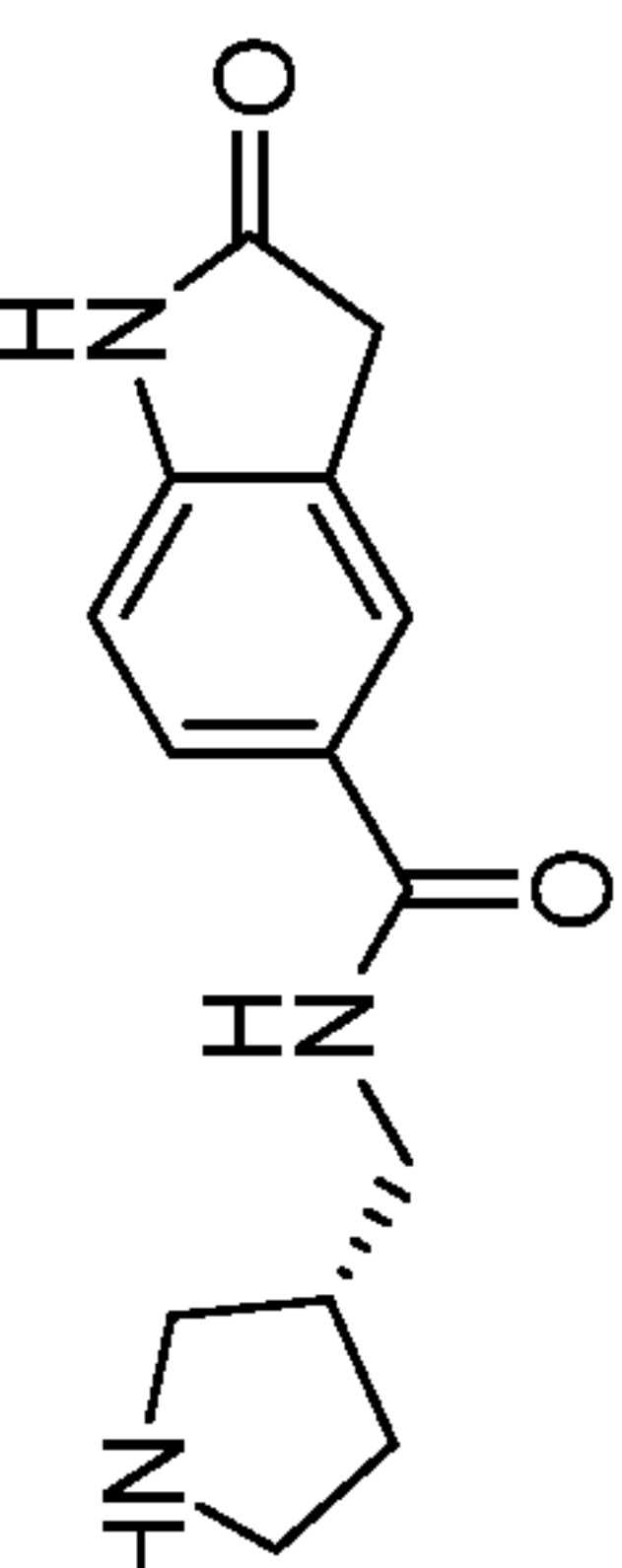
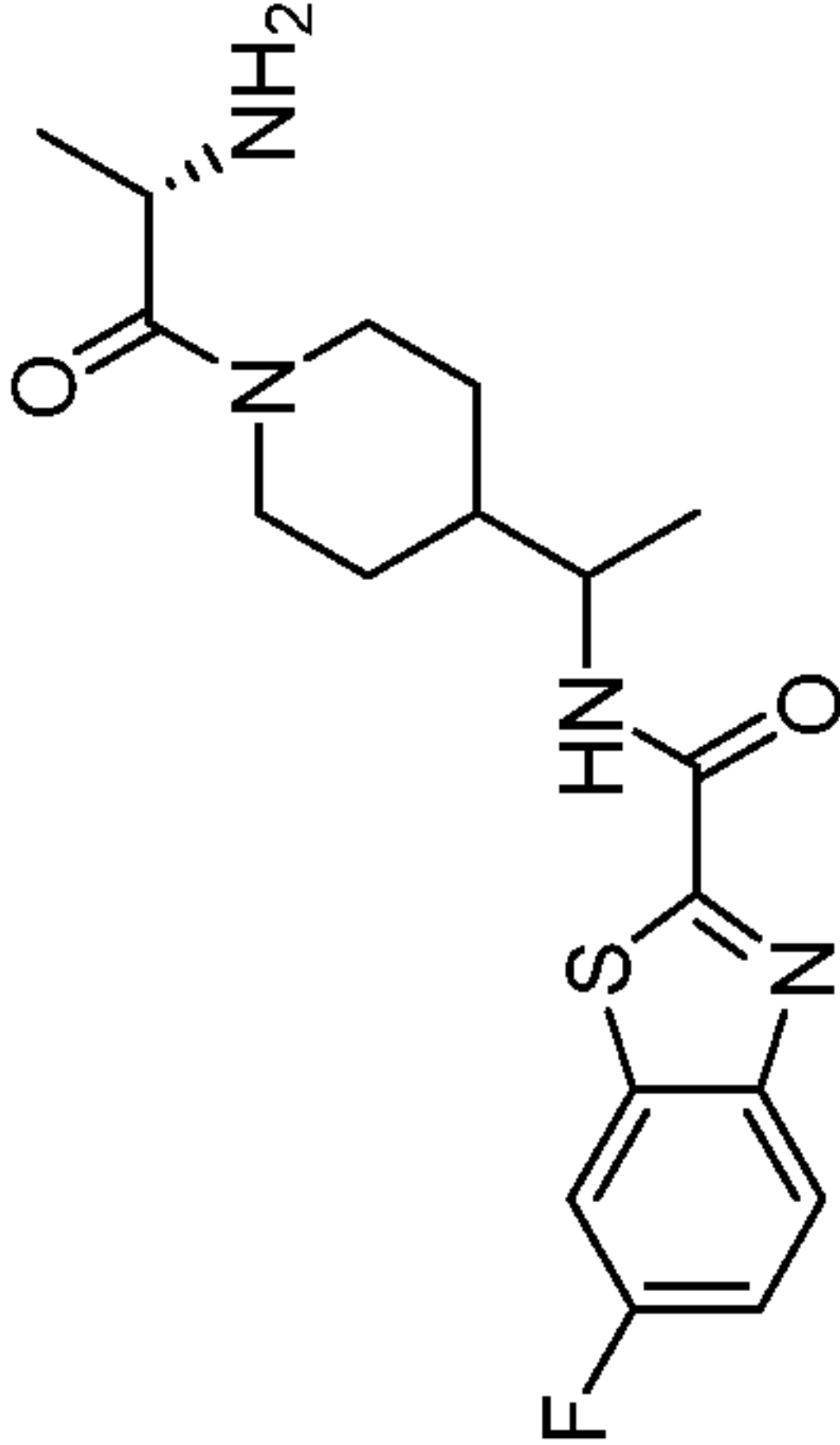
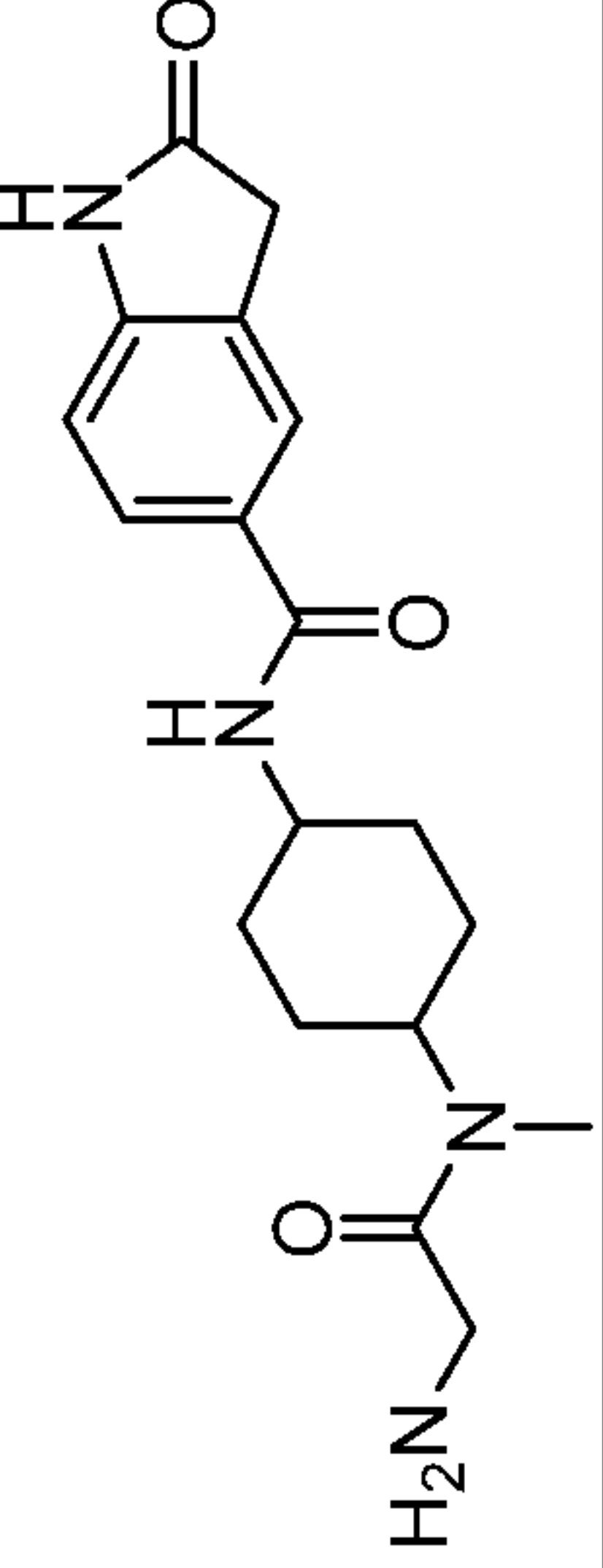
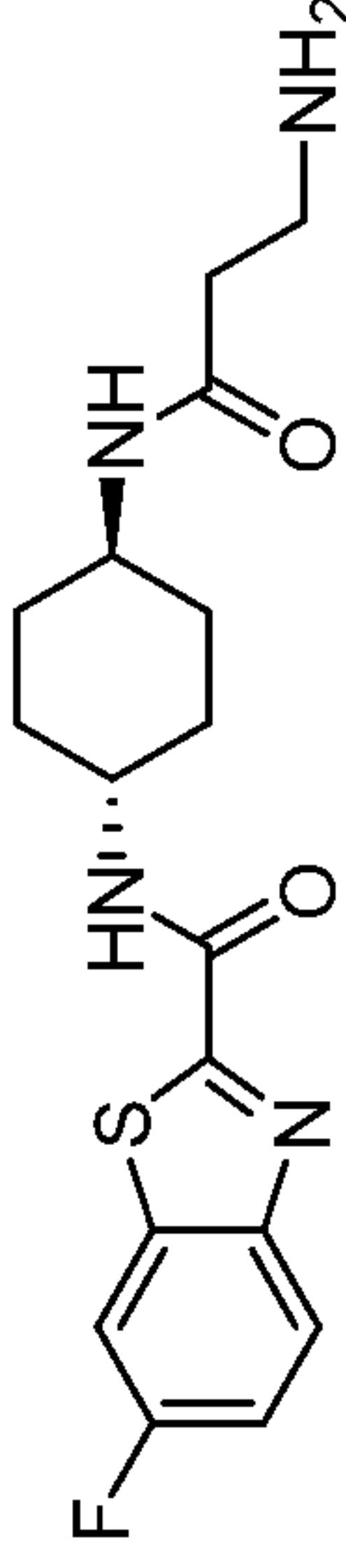
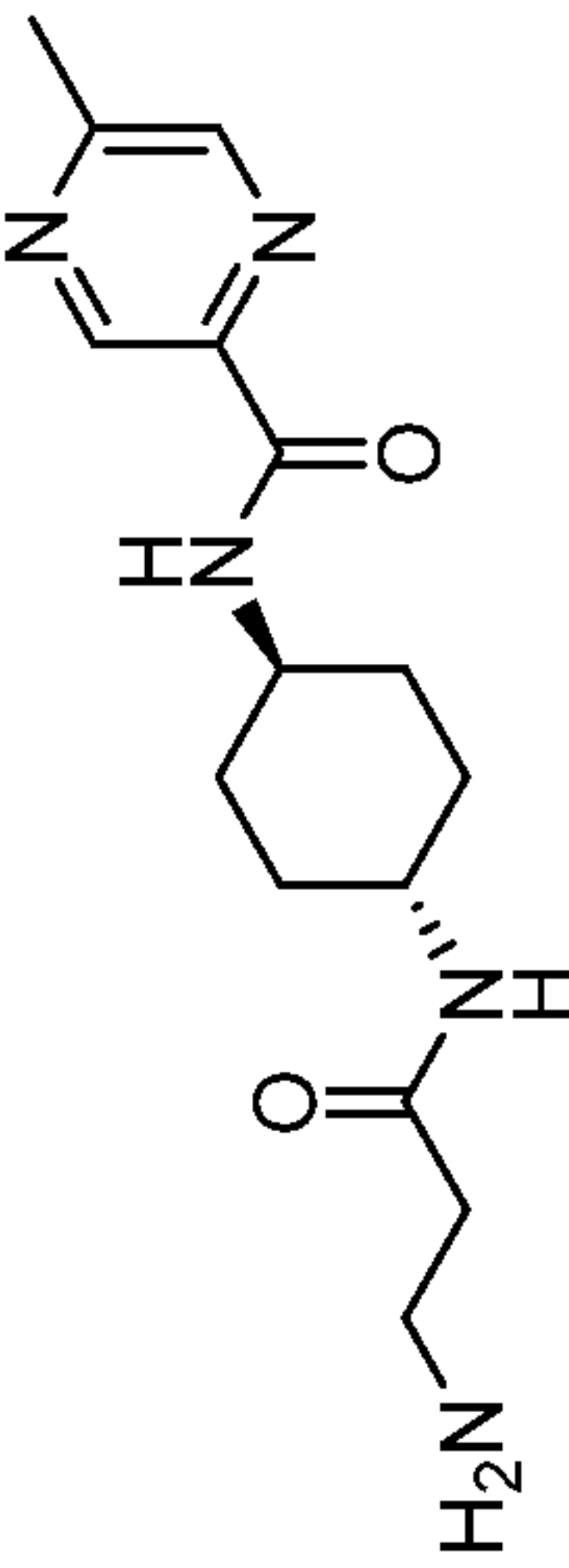
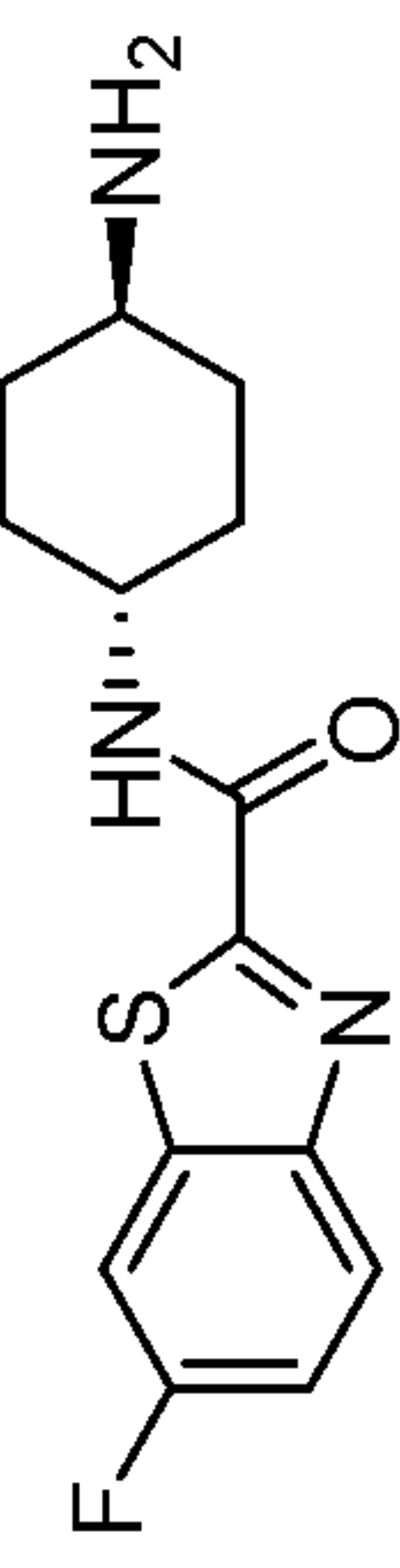
191		HCl	476		TFA
192		HCl	477		TFA
193		HCl	478		TFA
194		HCl	479		TFA

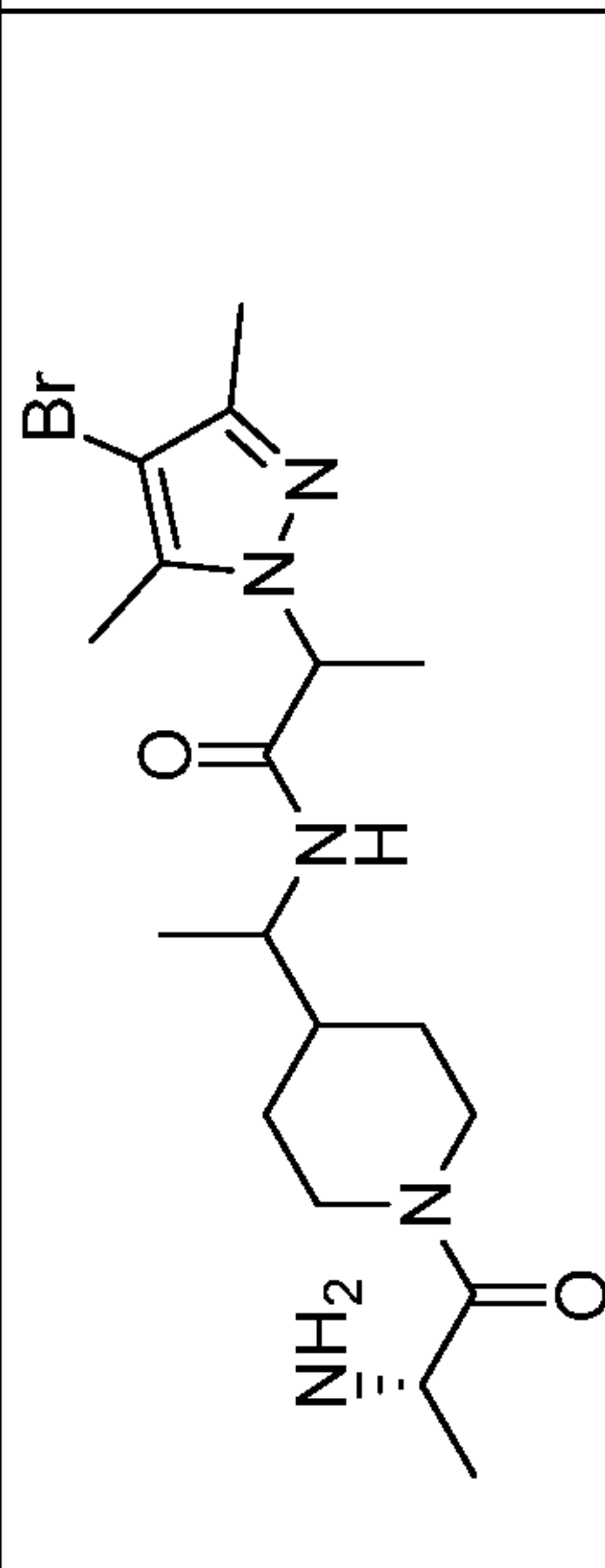
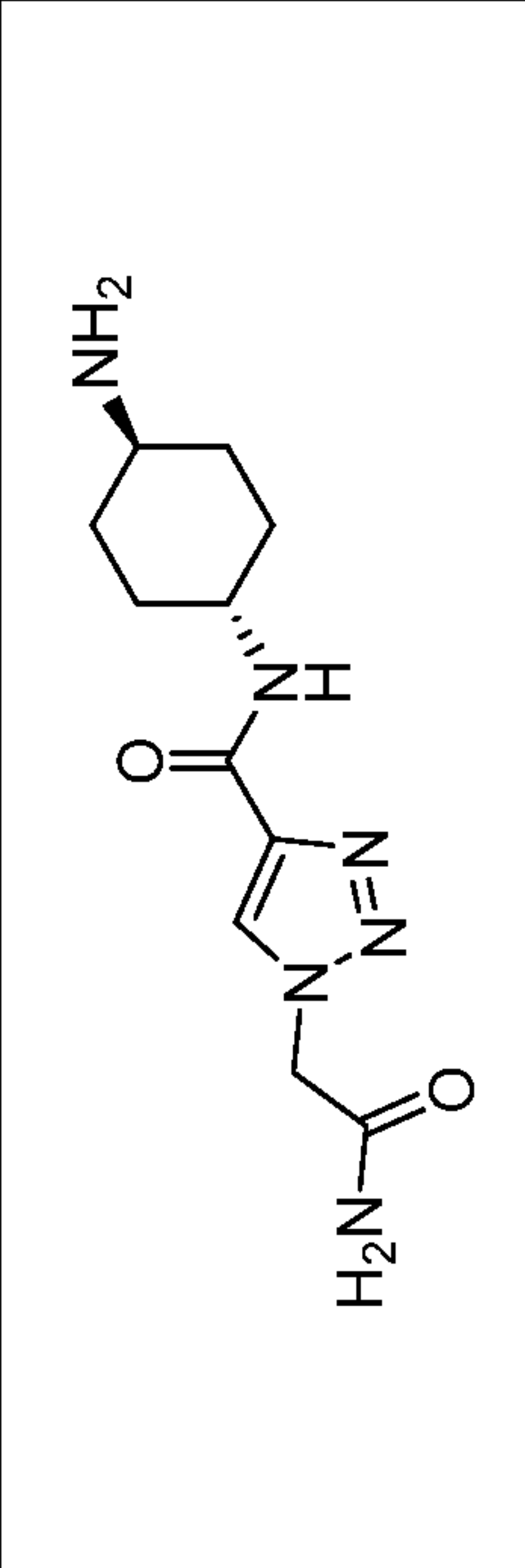
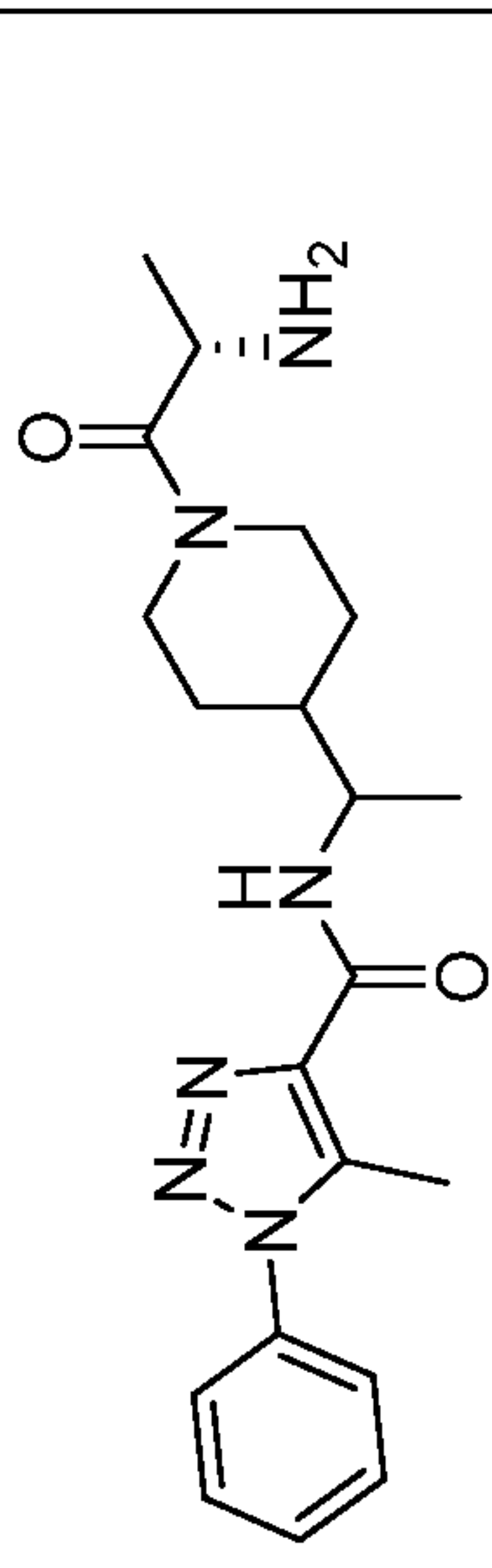
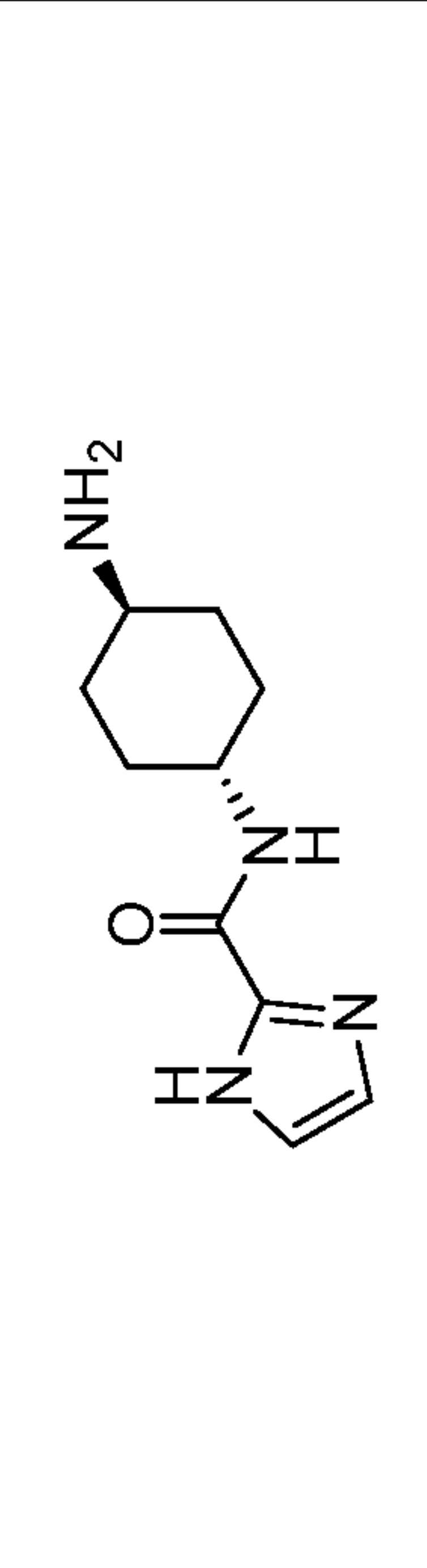
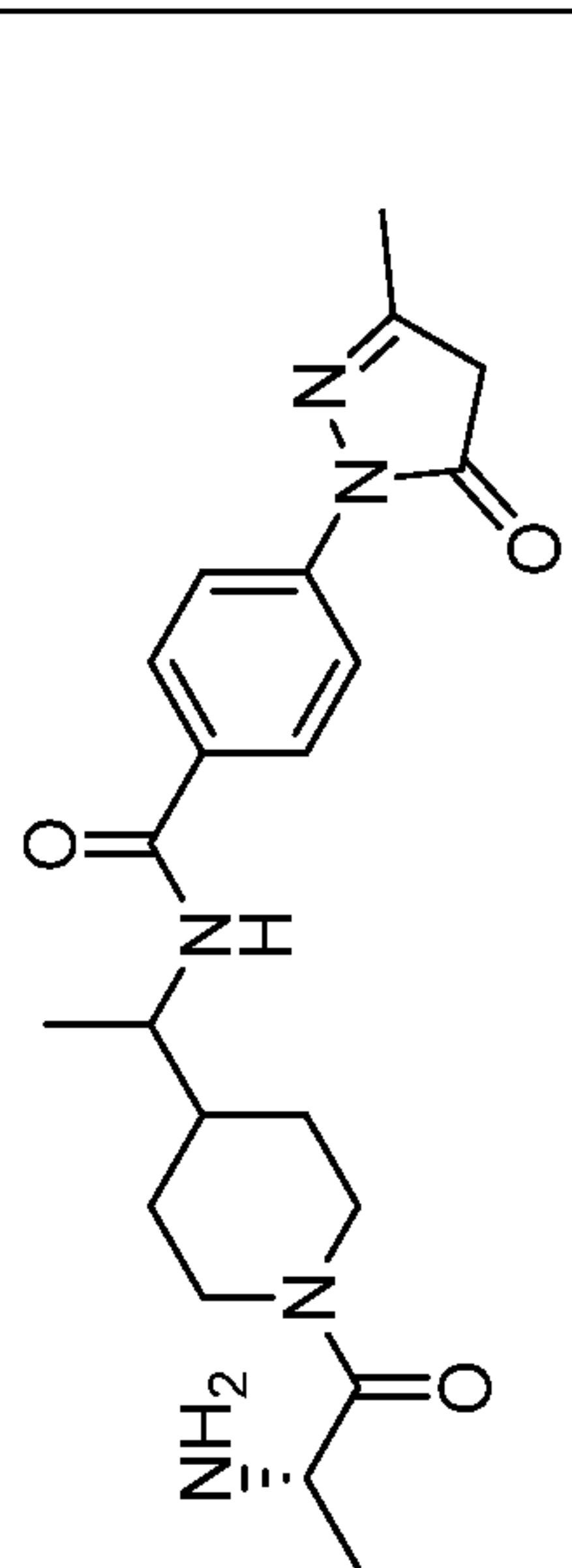
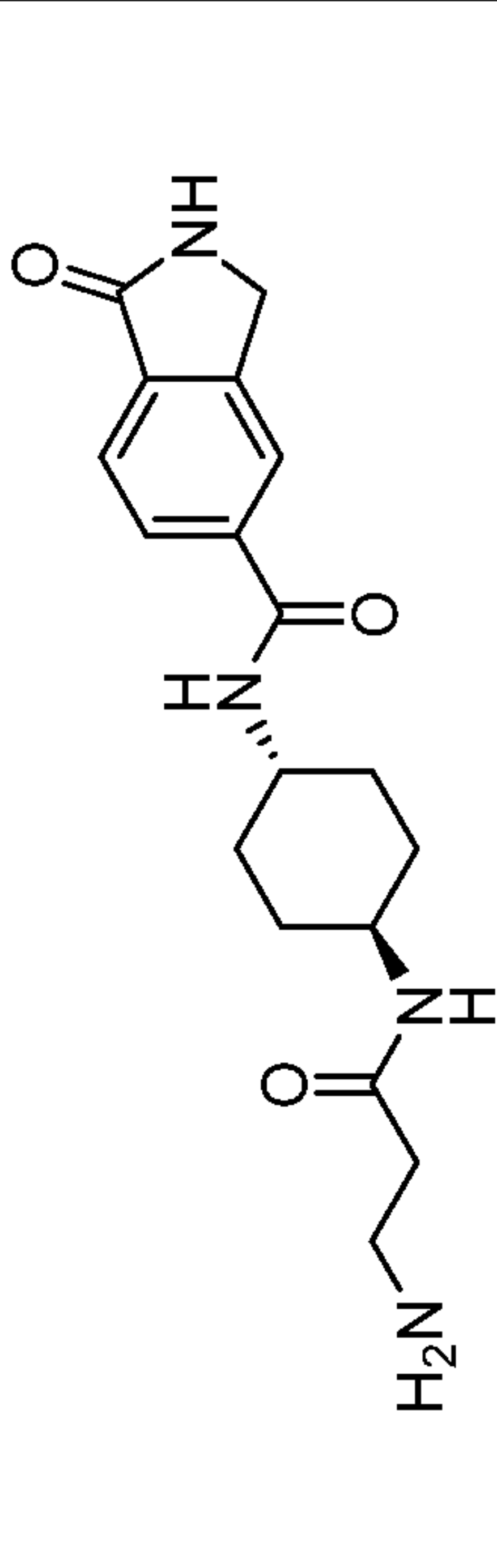
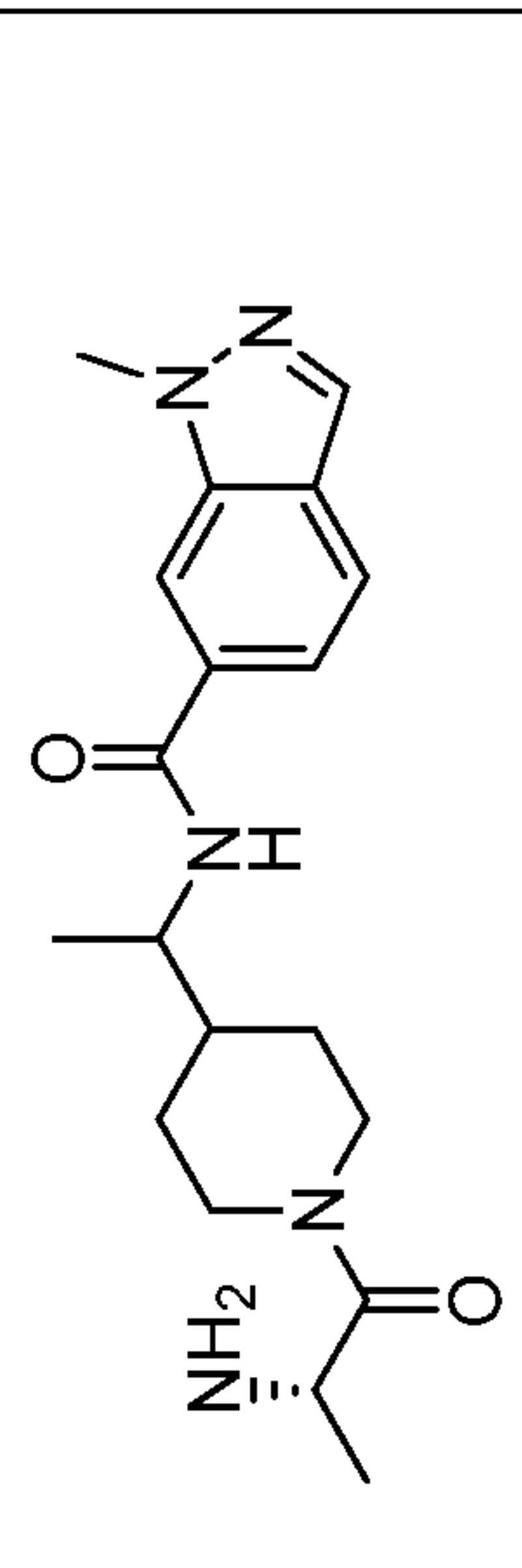
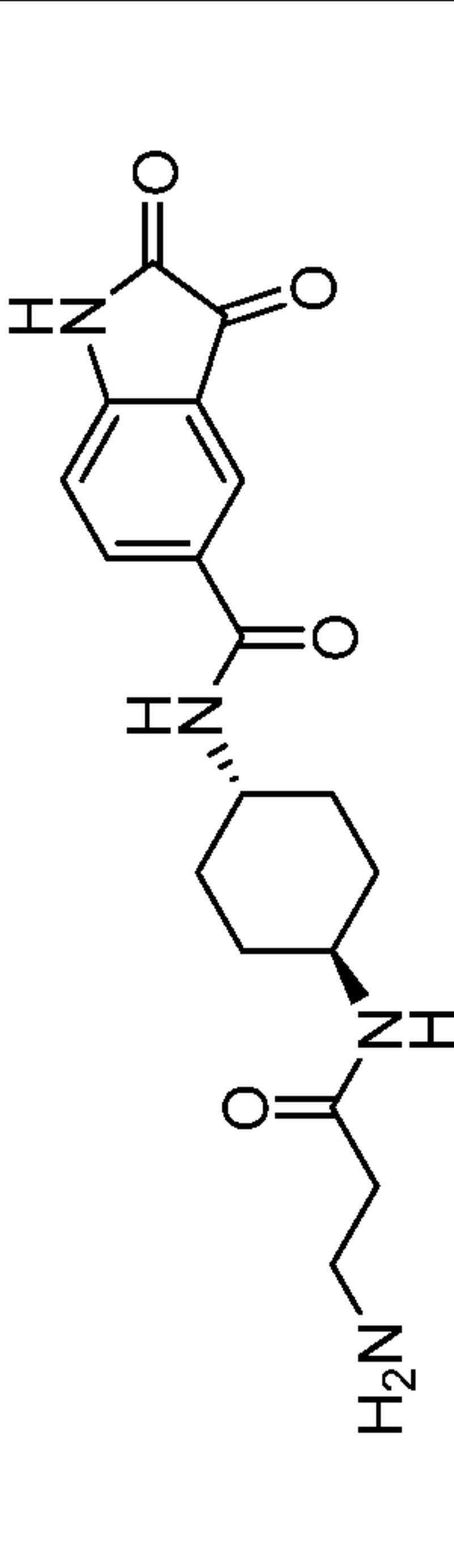
195		HCl	480		TFA
196		TFA	481		TFA
197		TFA	482		TFA

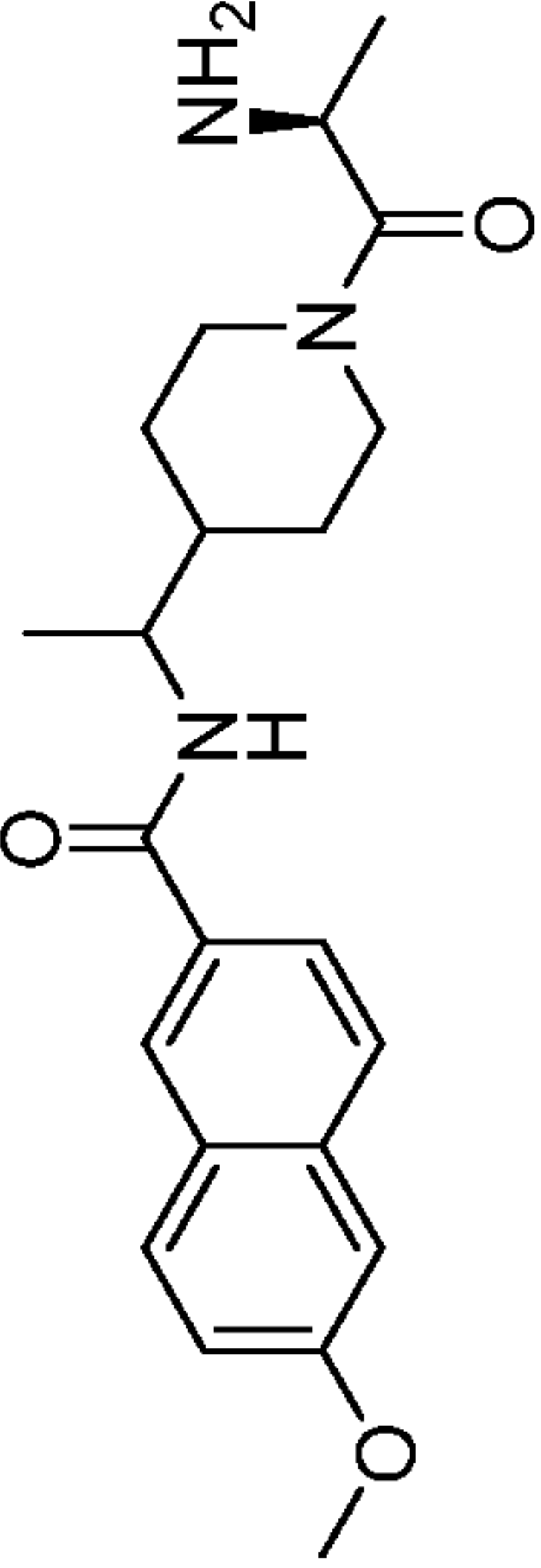
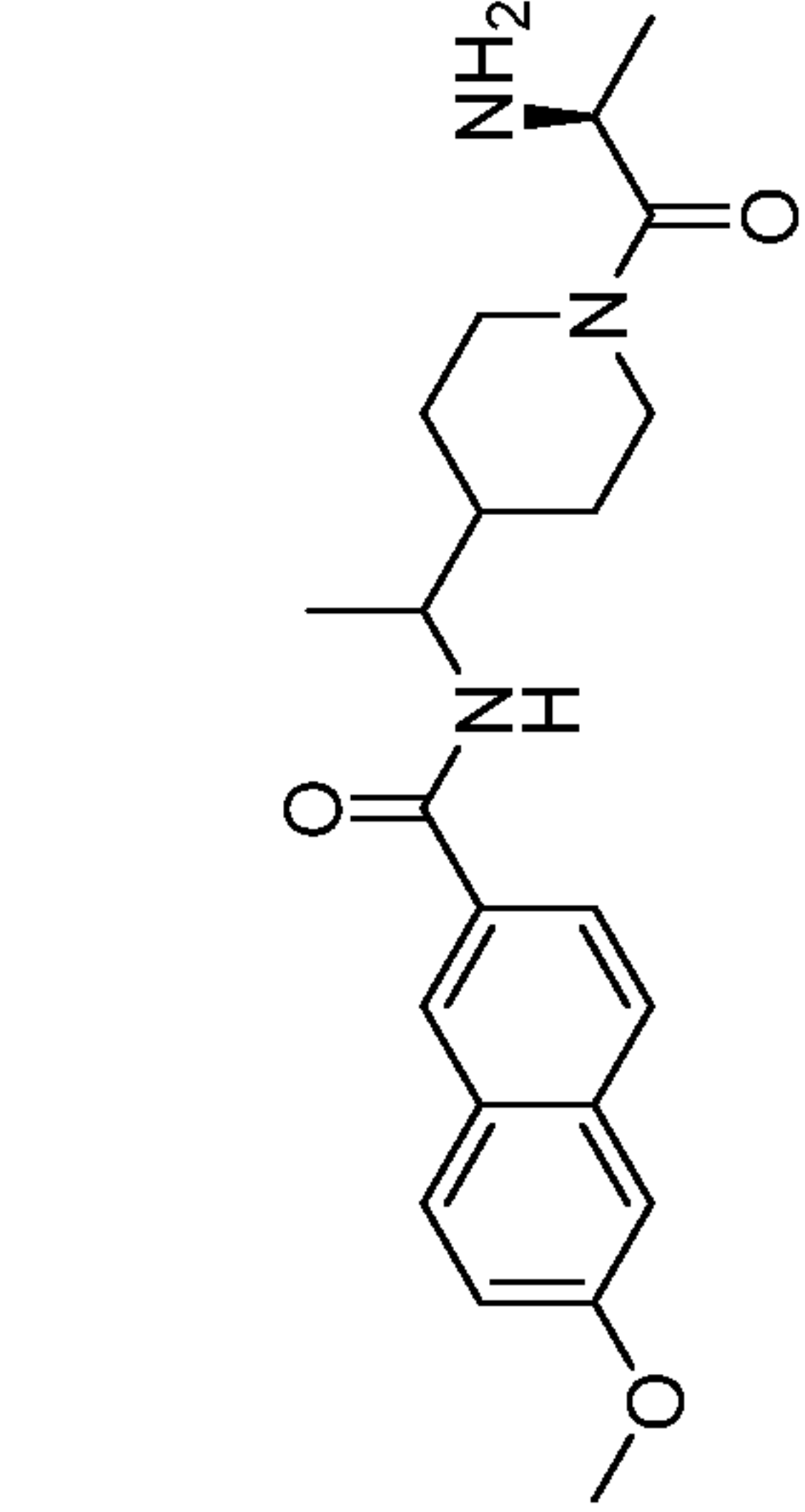
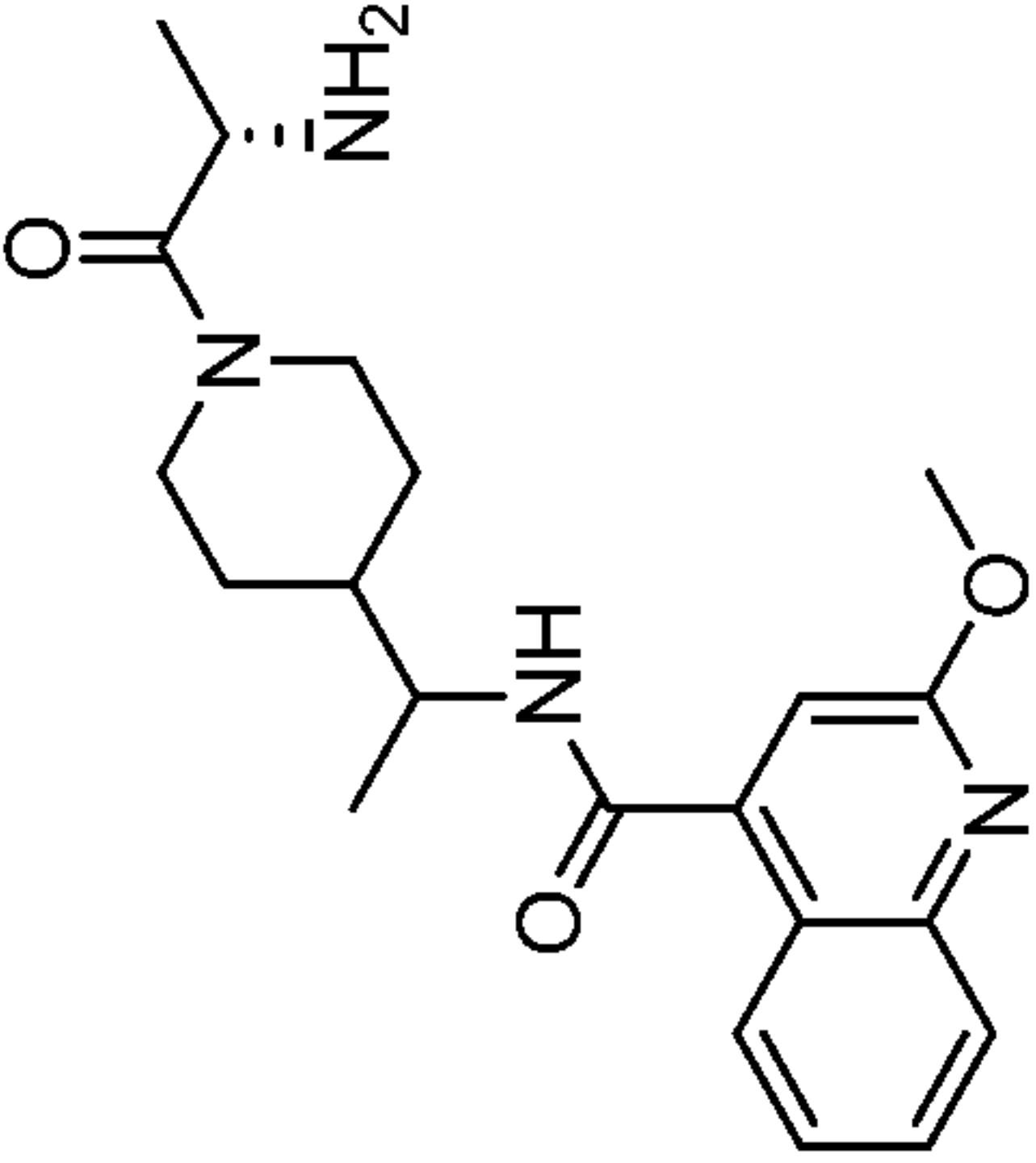
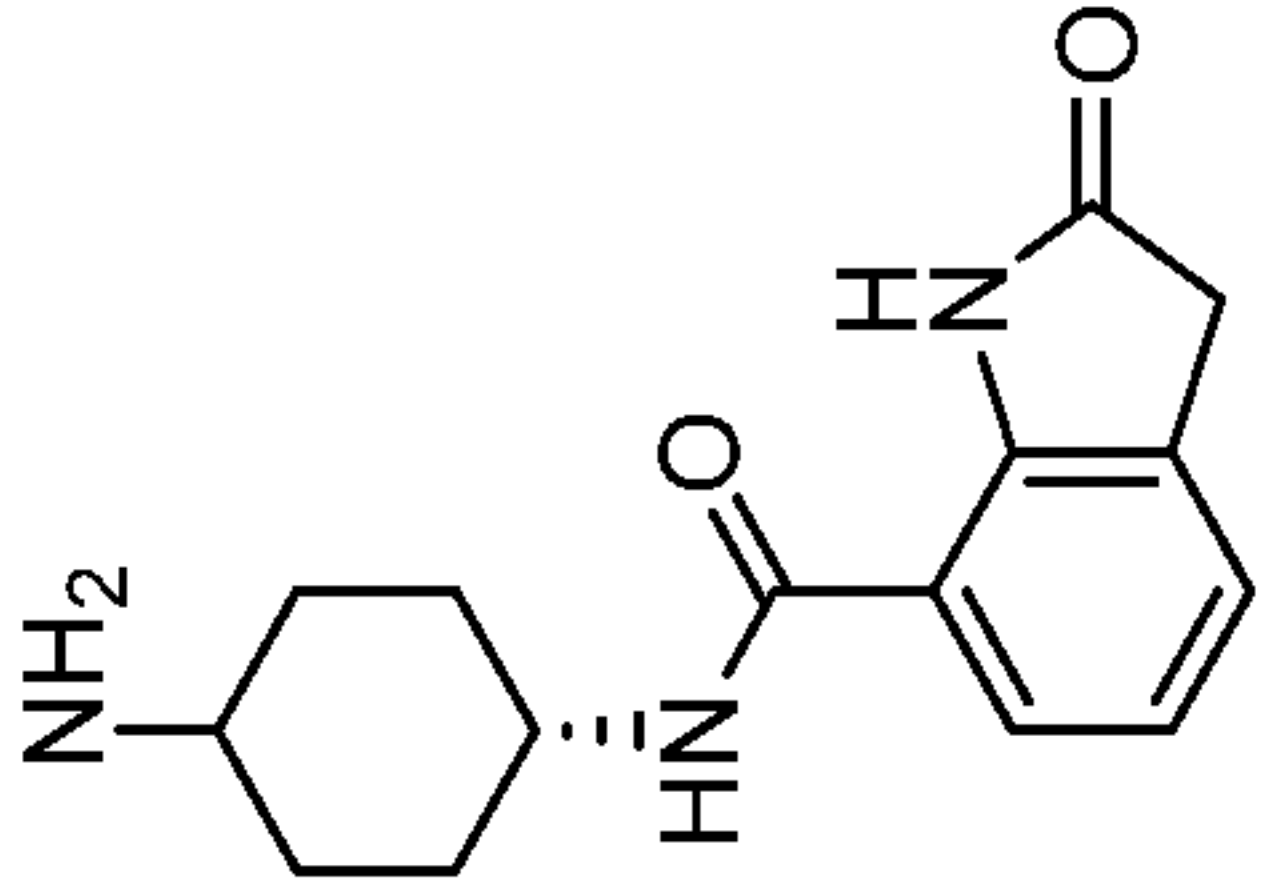
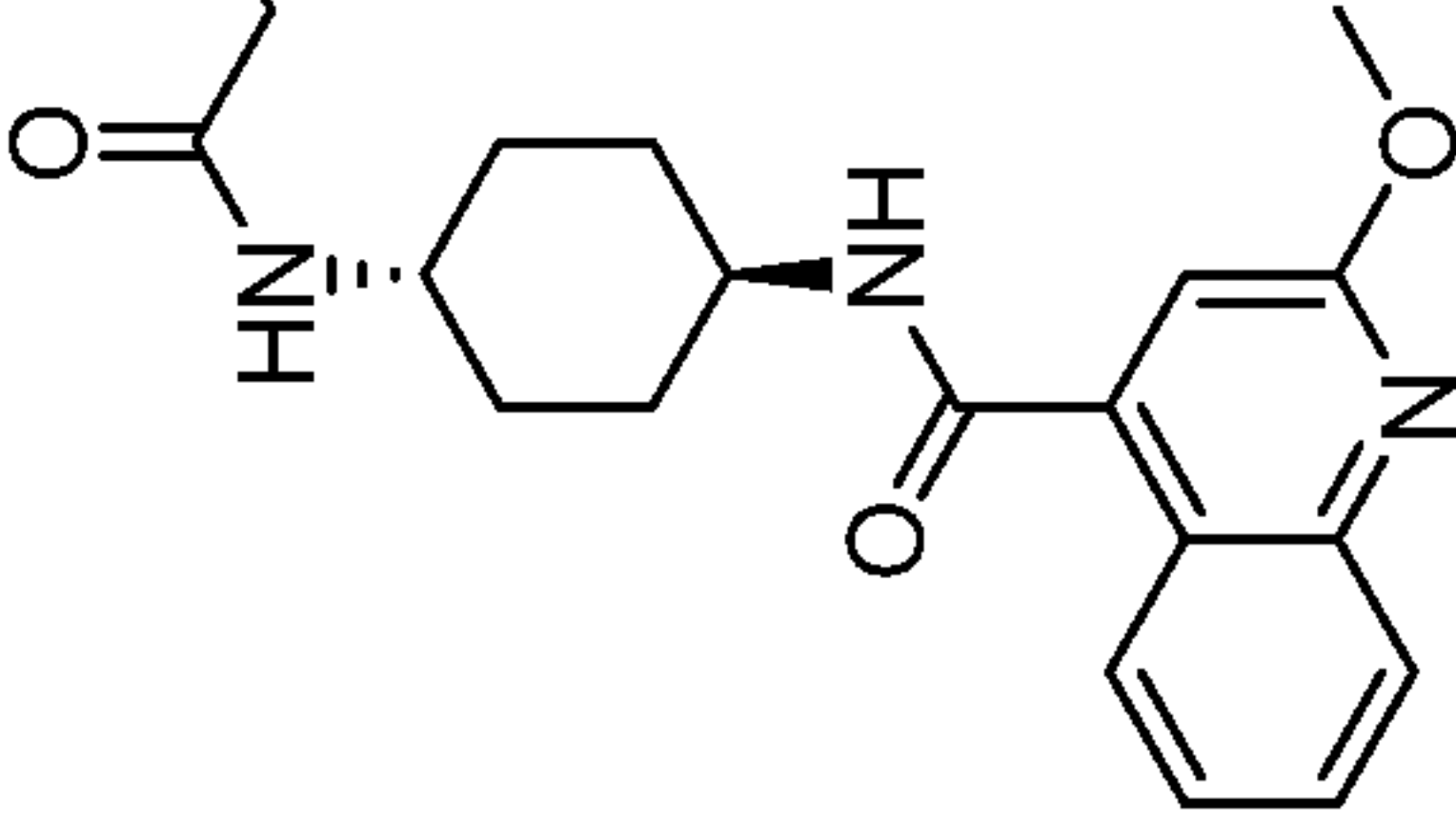
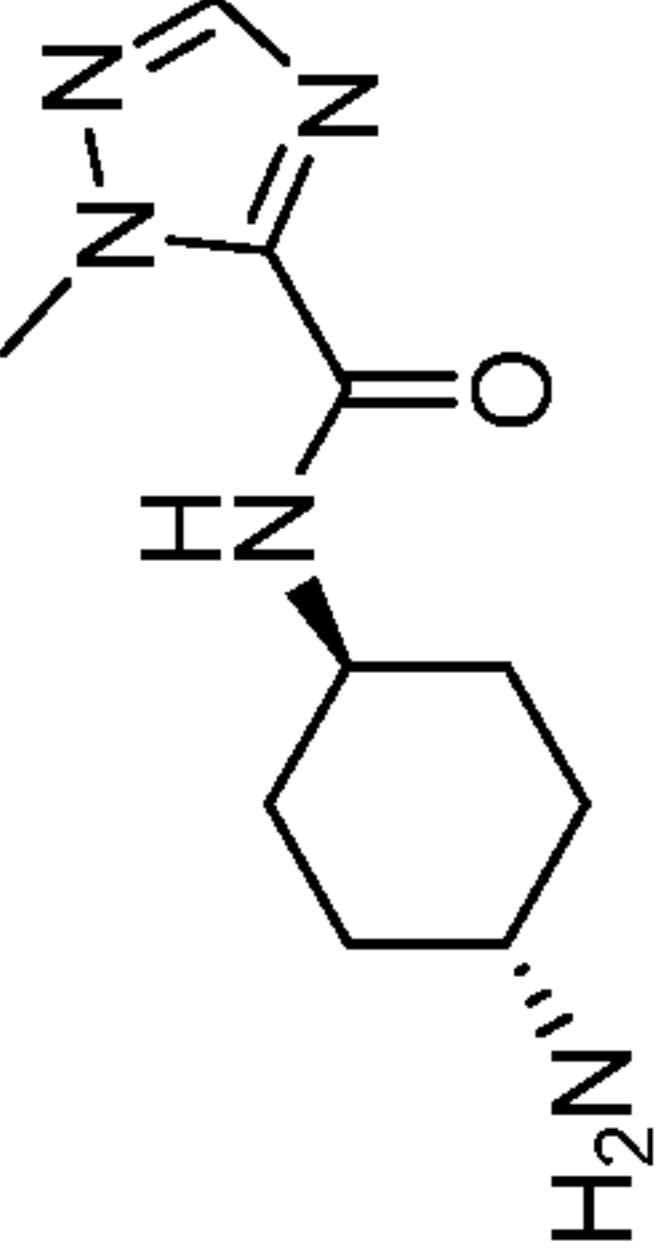
198		TFA	483		TFA
199		HCl	484		None
200		TFA	485		None

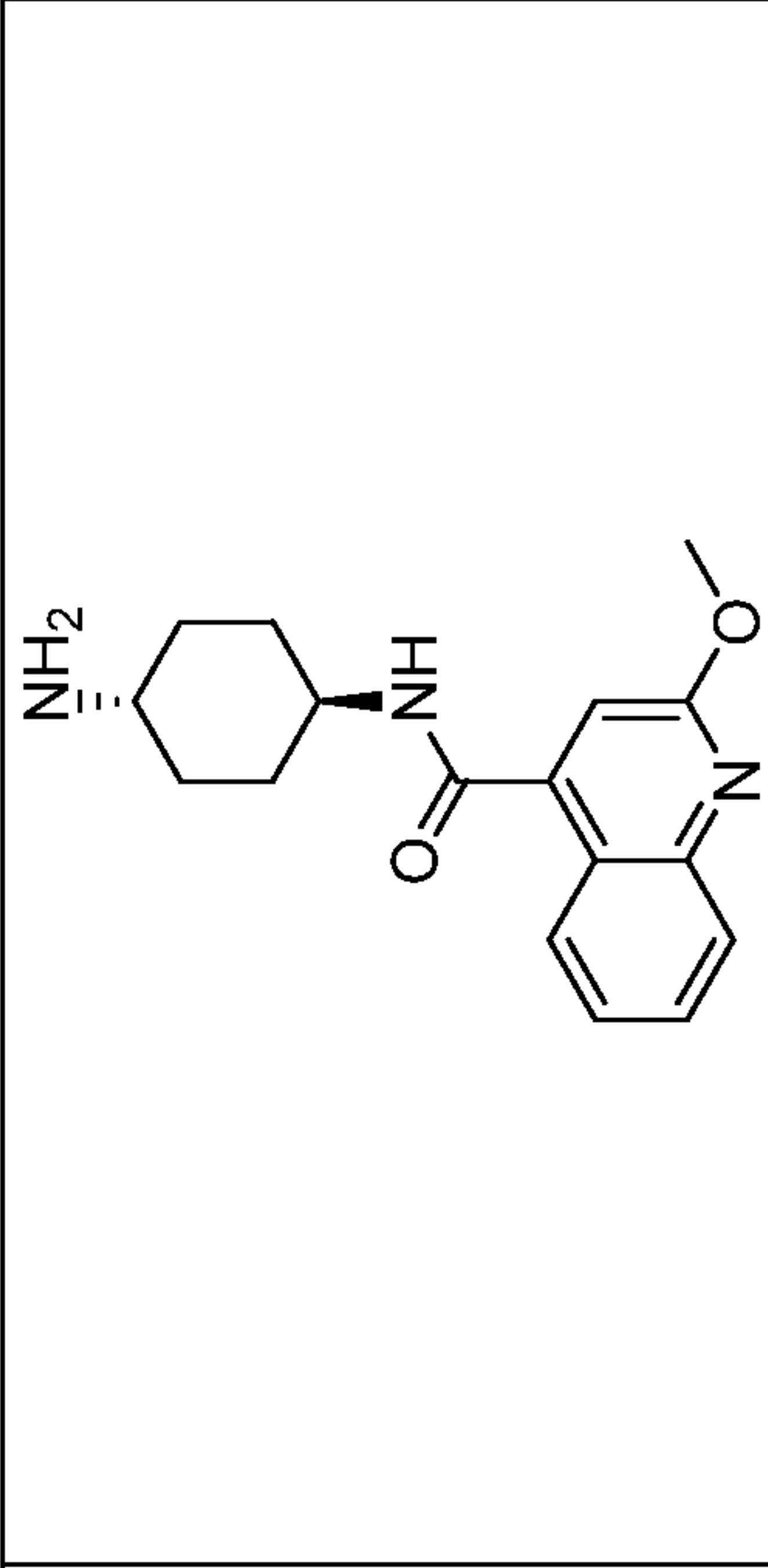
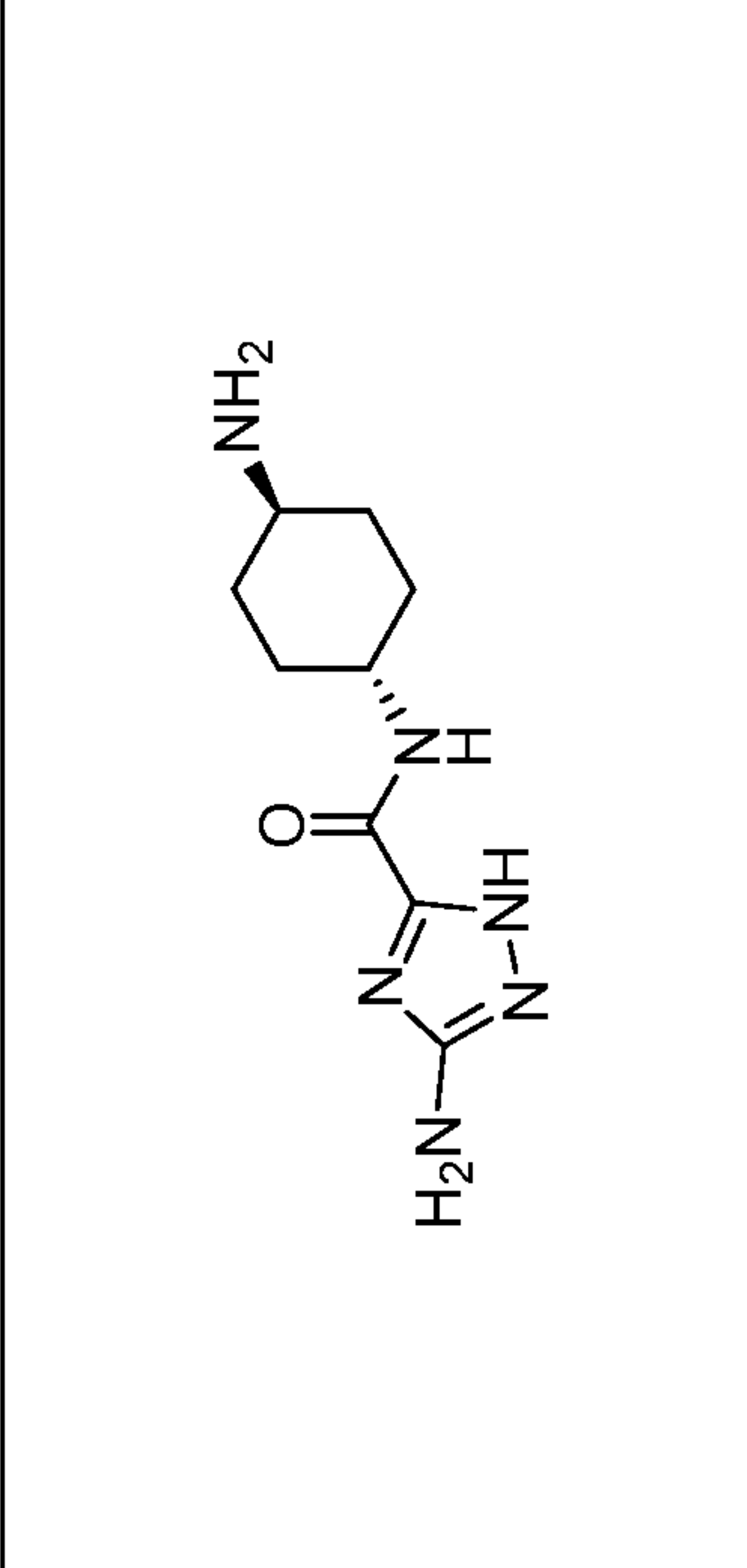
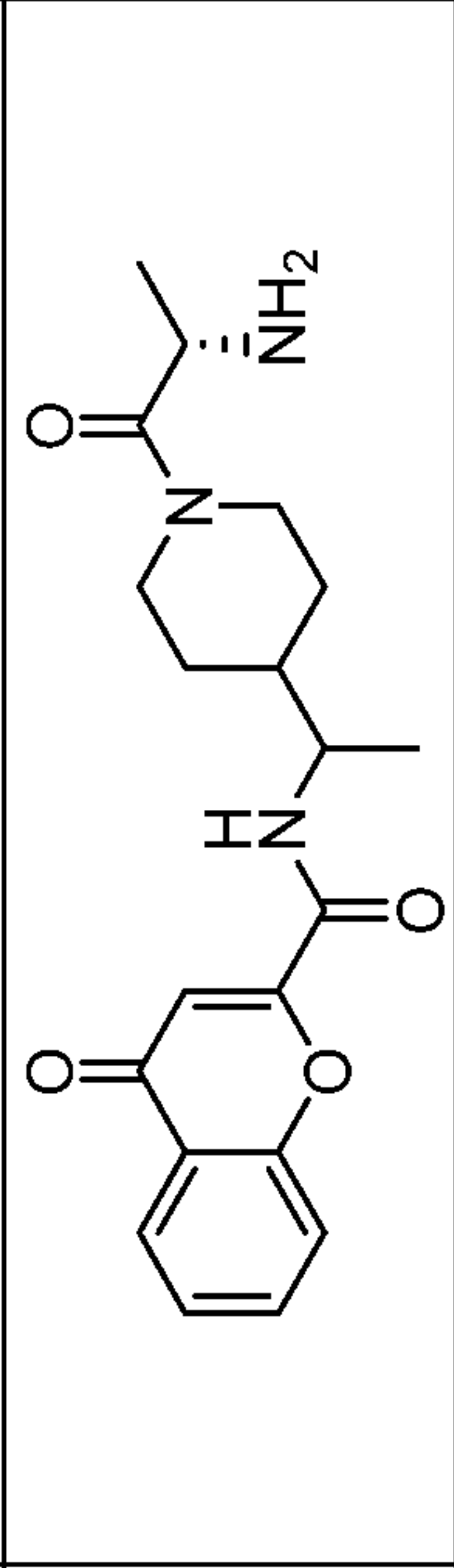
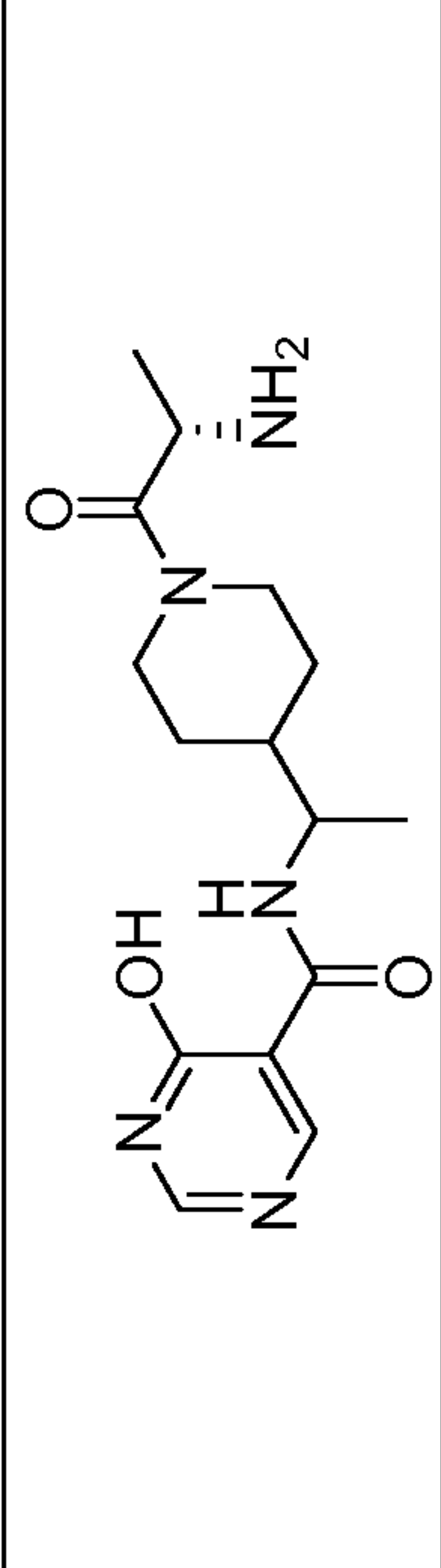
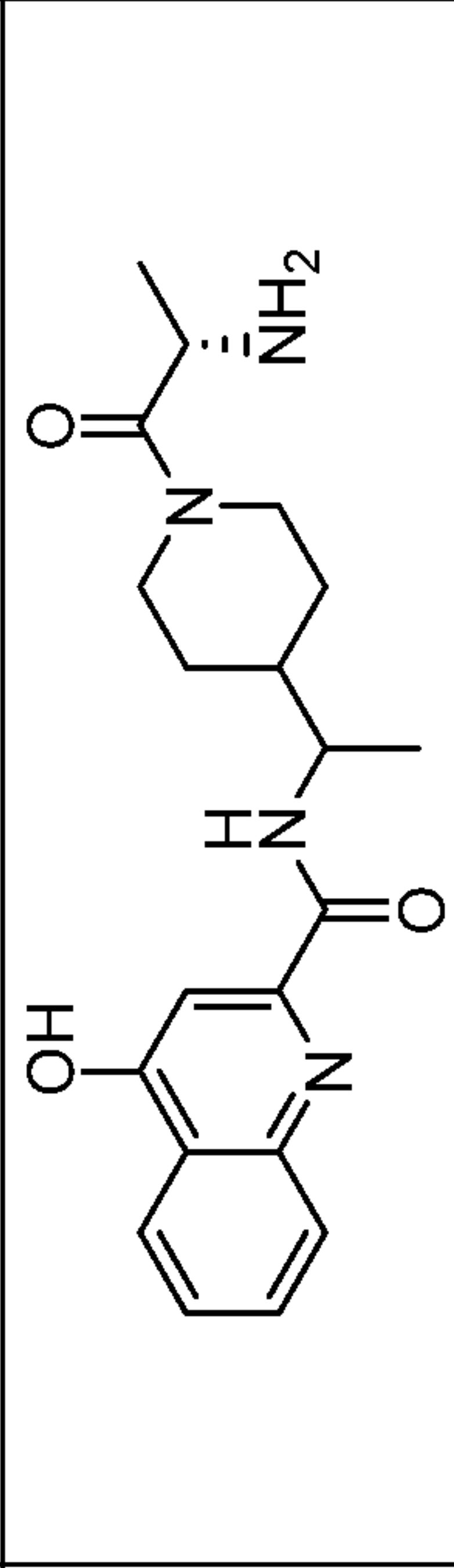
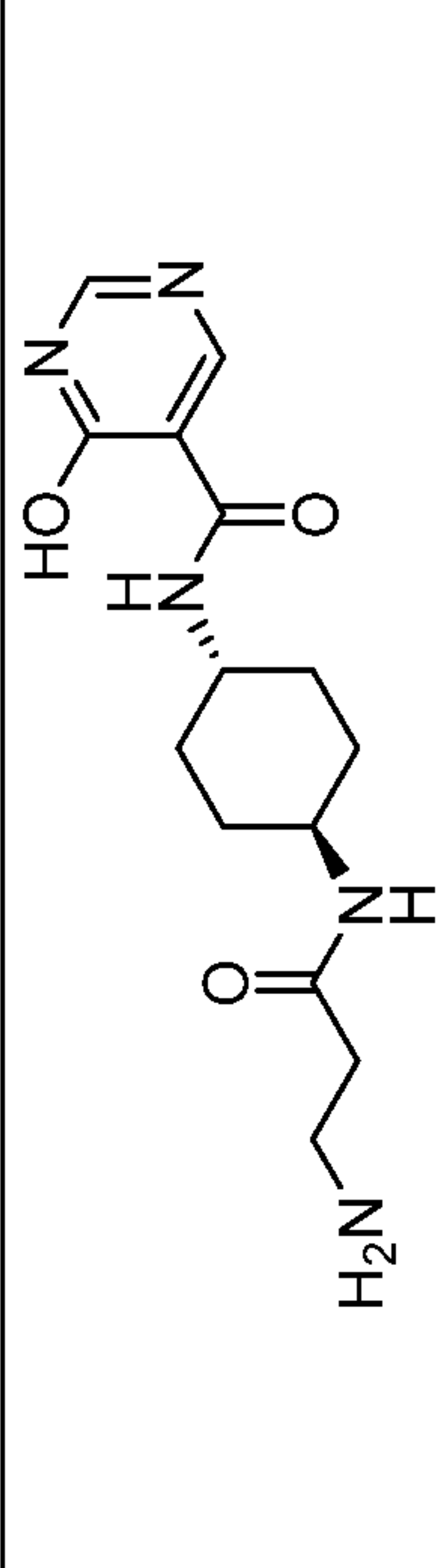
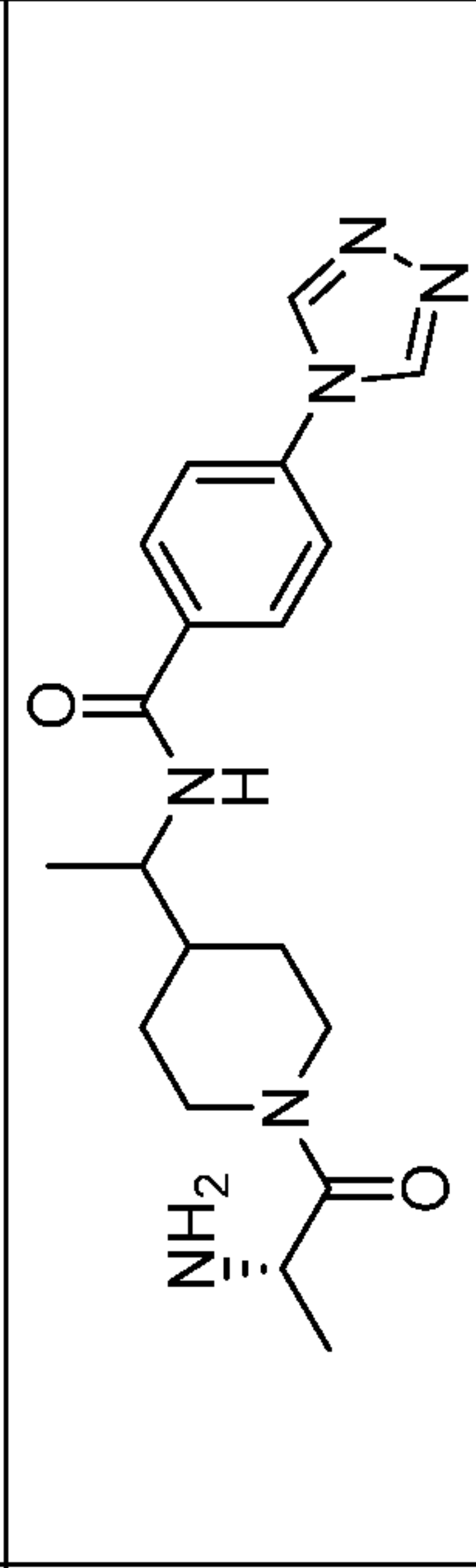
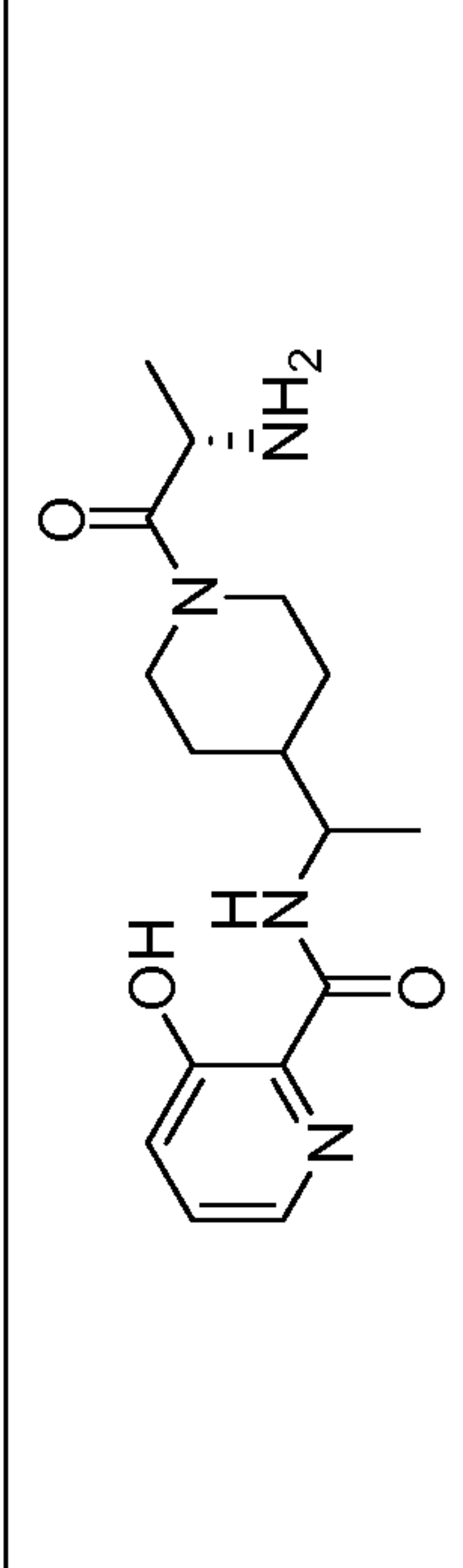
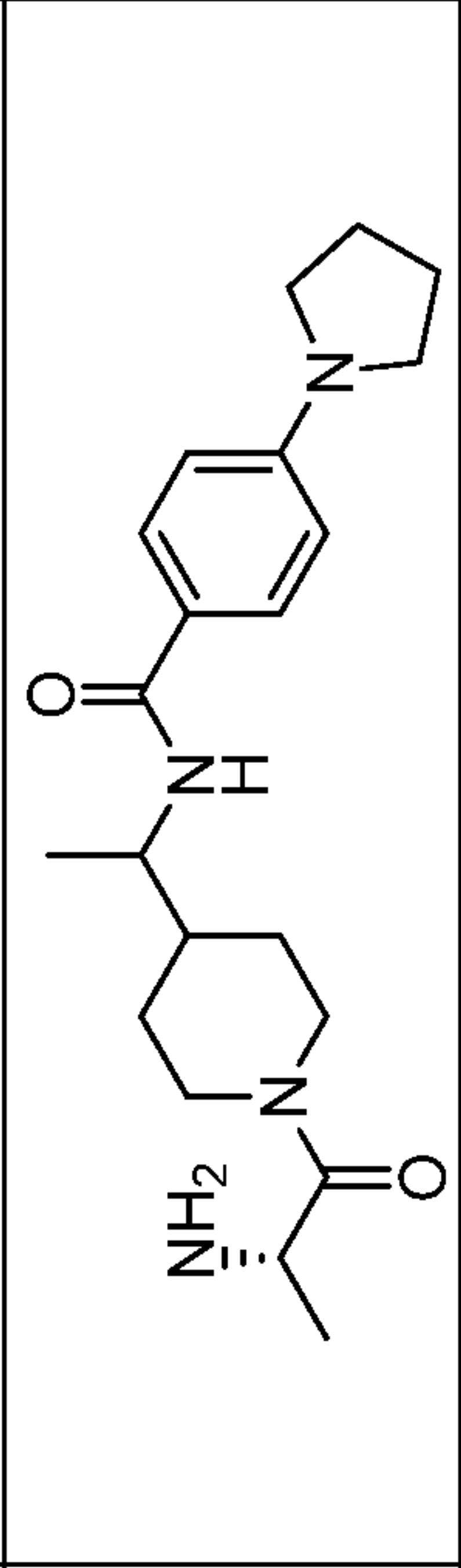
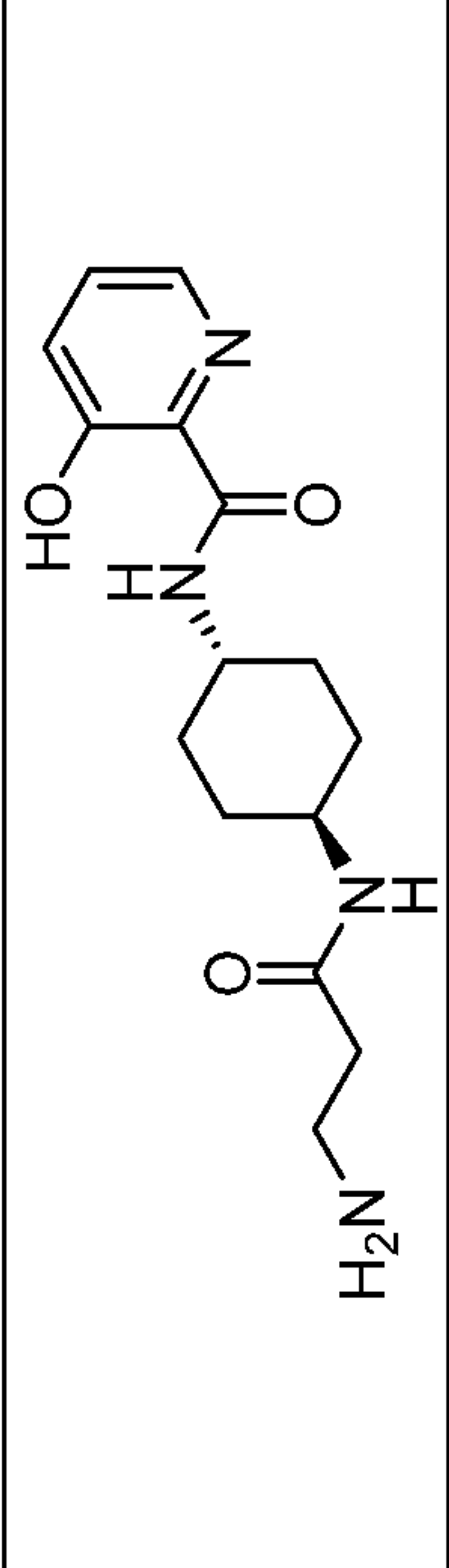
201		TFA	486		TFA
202		HCl	487		TFA
203		HCl	488		TFA
204		HCl	489		TFA

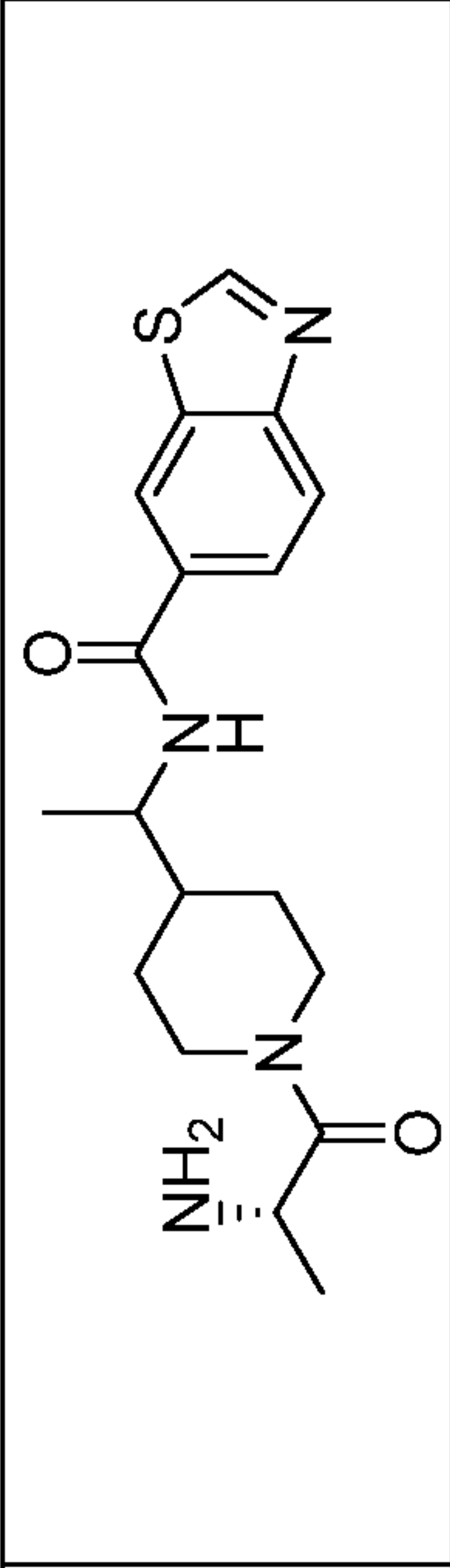
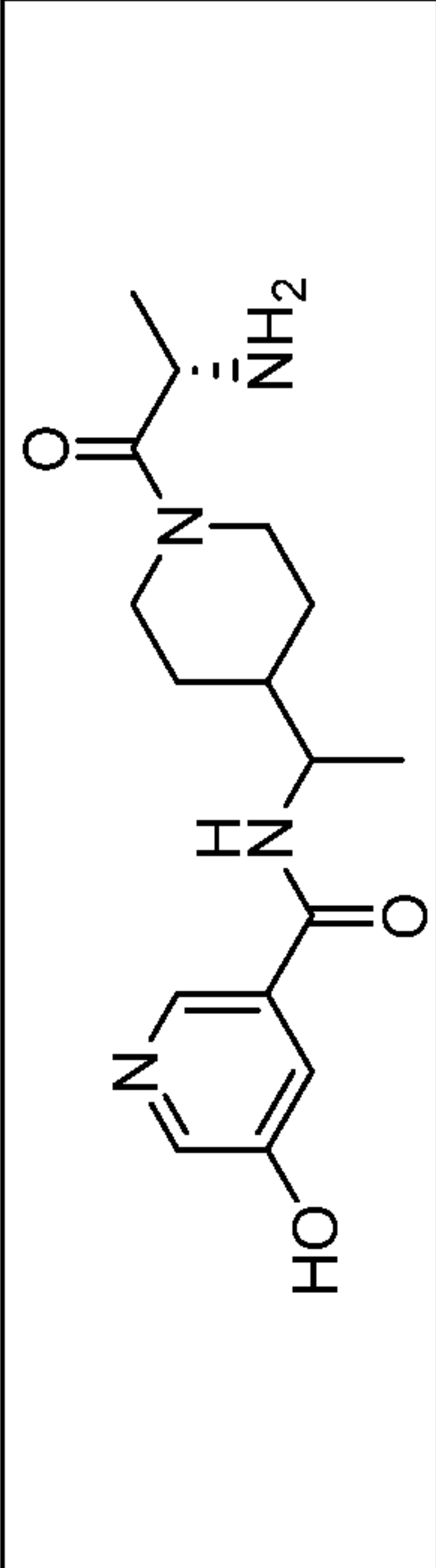
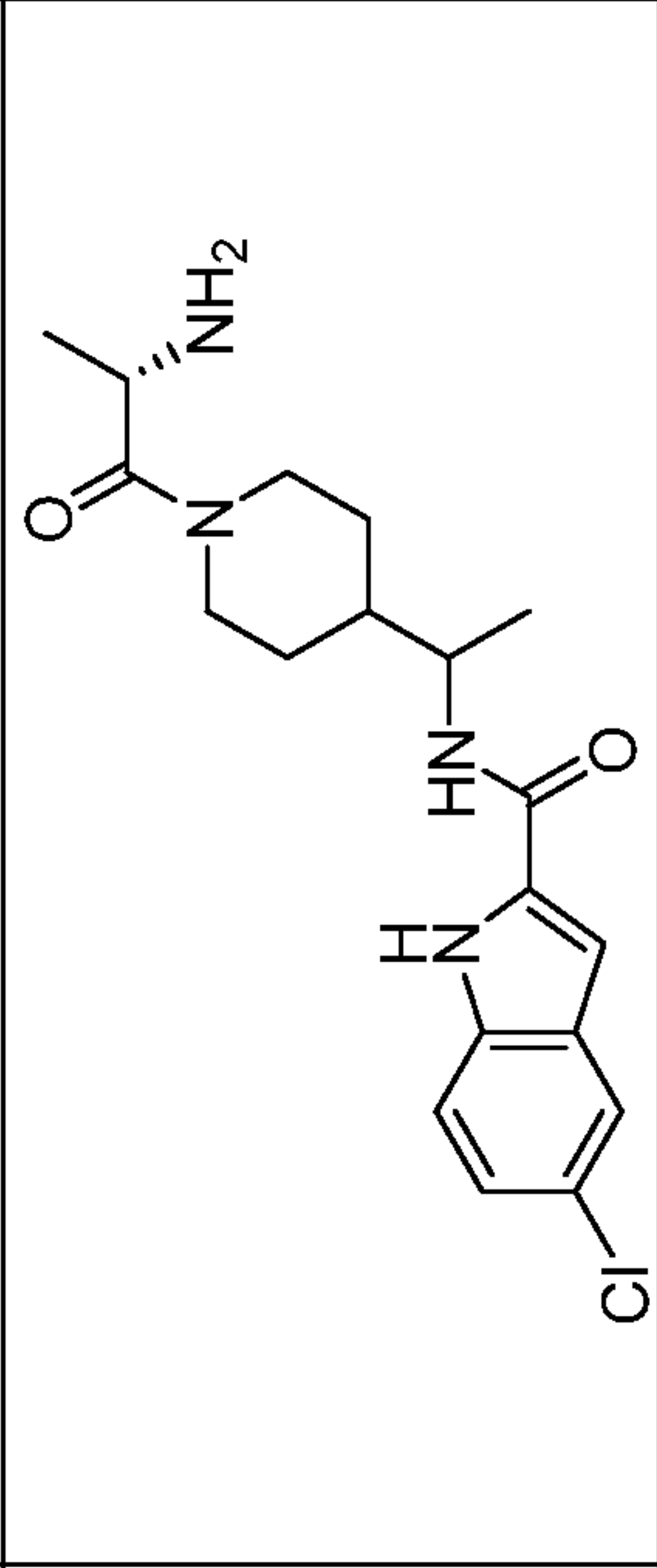
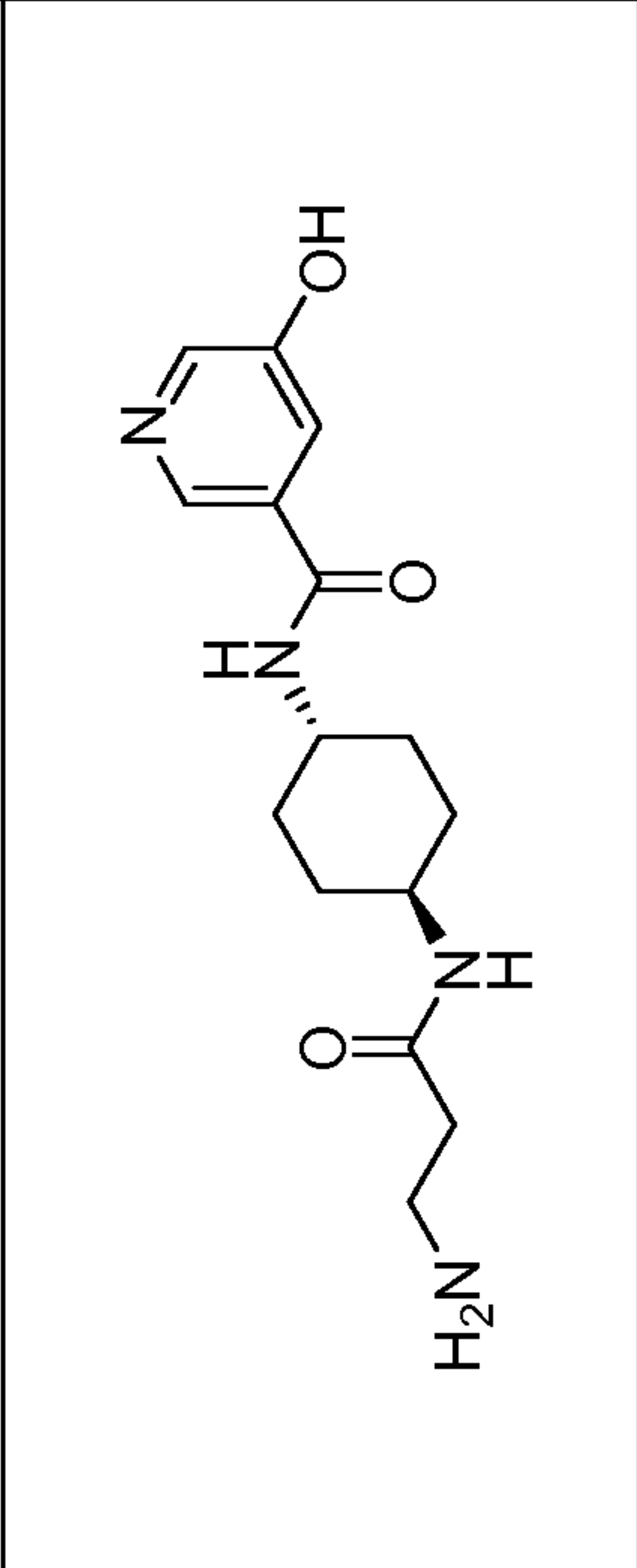
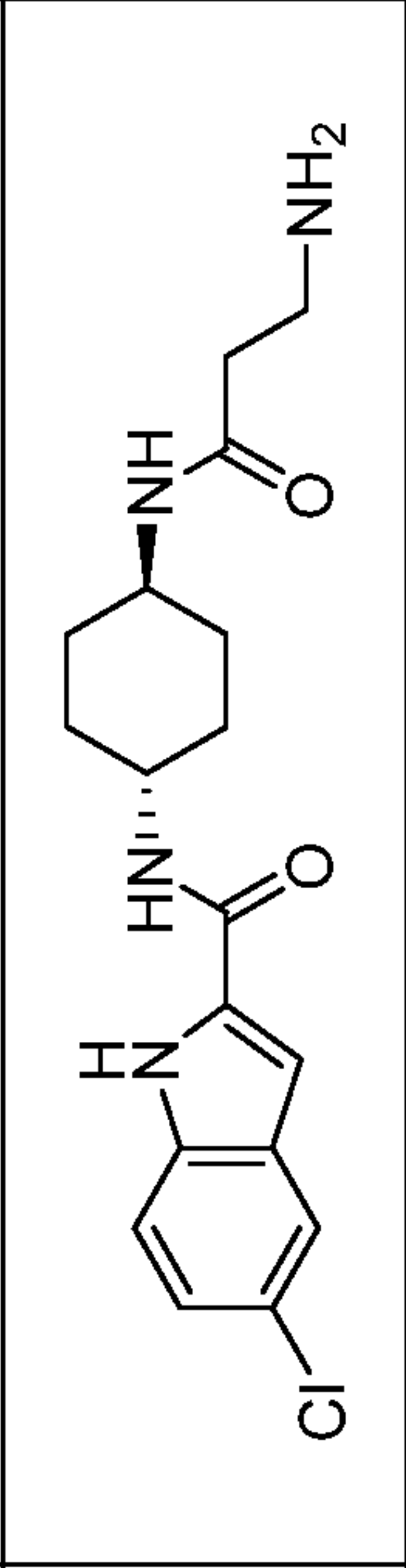
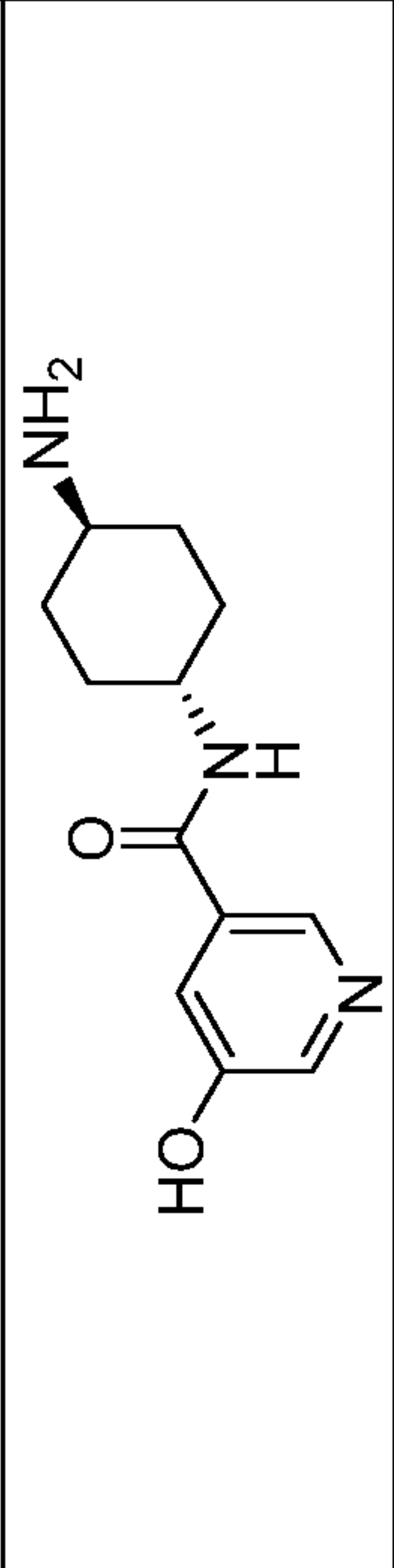
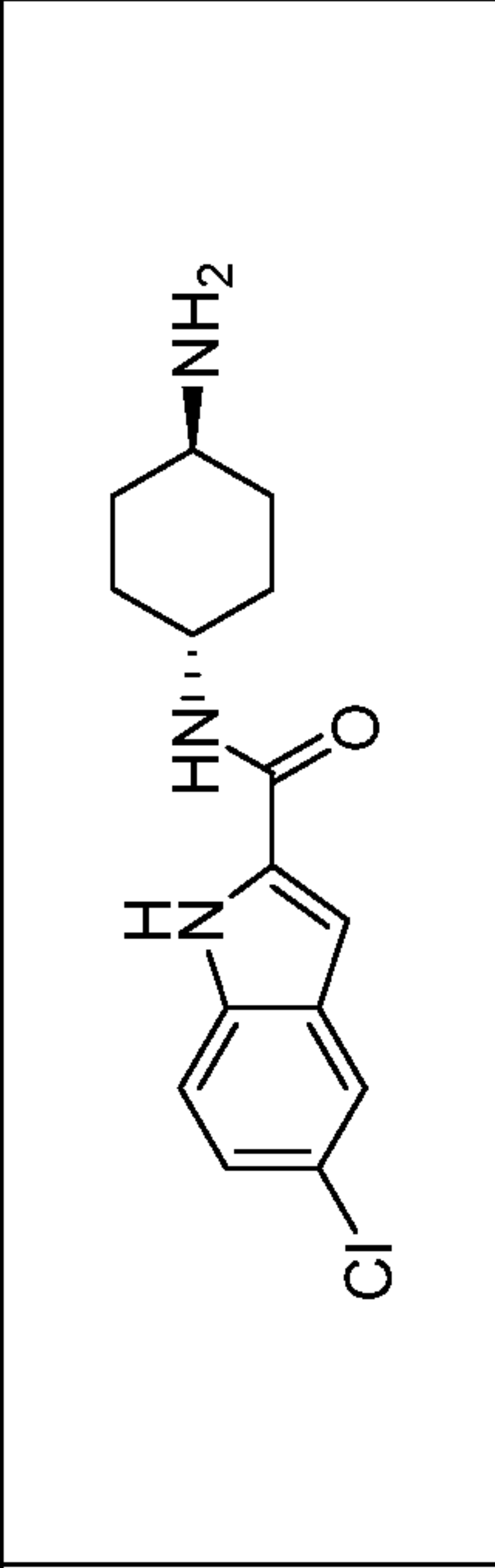
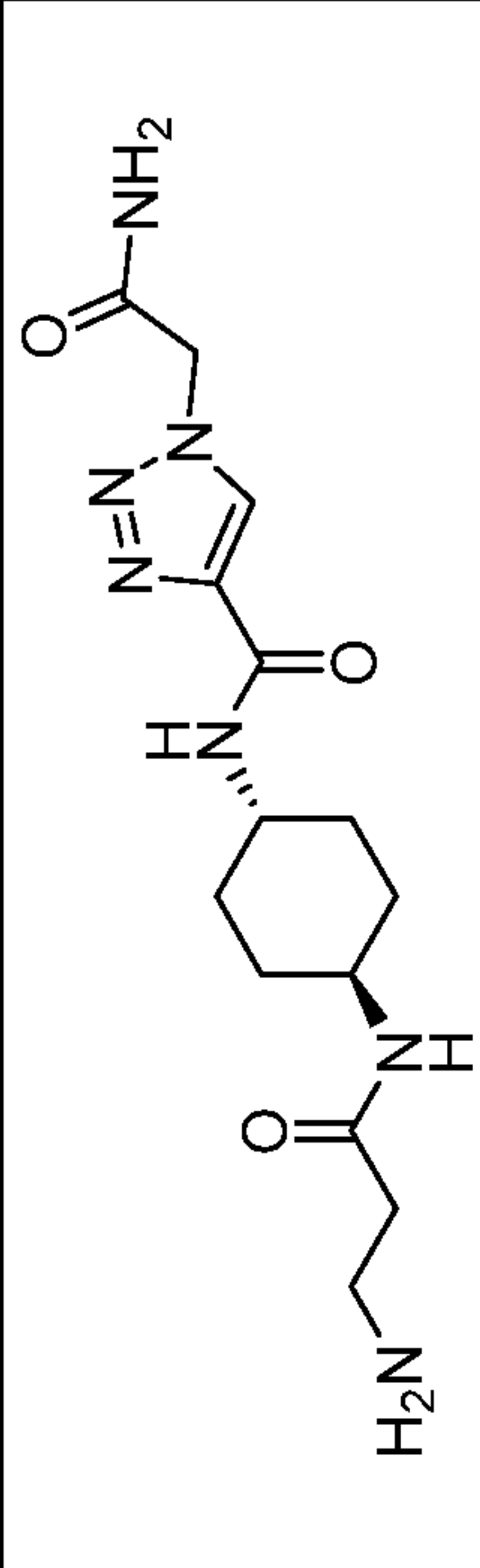
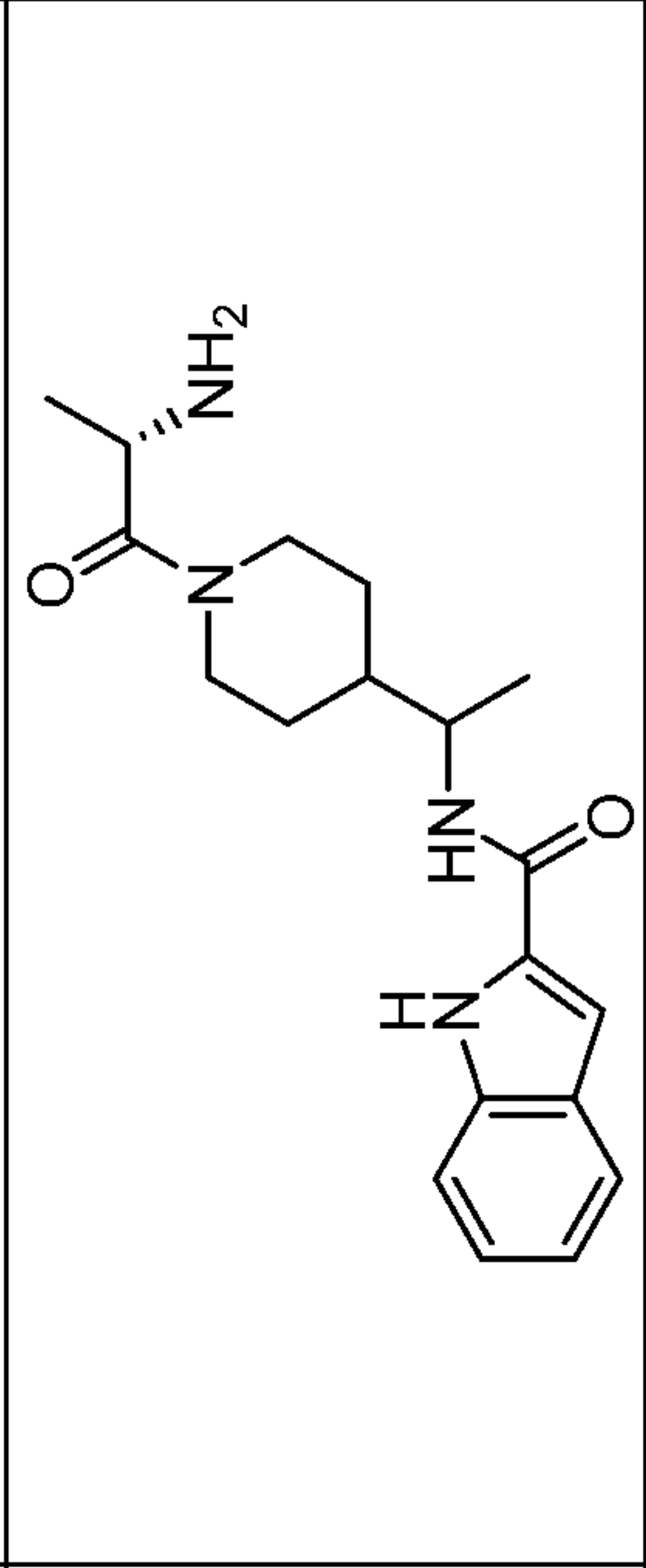
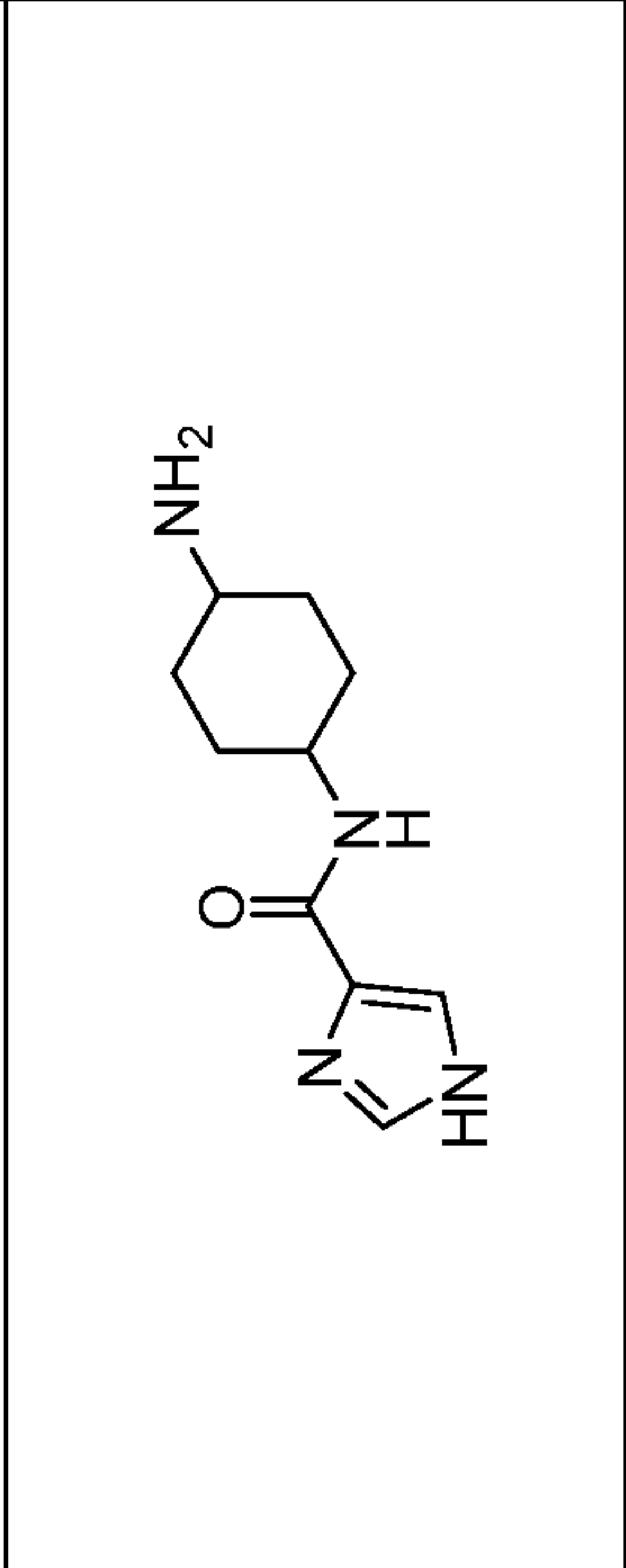
205		HCl	490		TFA
206		HCl	491		TFA
207		HCl	492		None
208		TFA	493		TFA
209		HCl	494		None
210		HCl	495		None

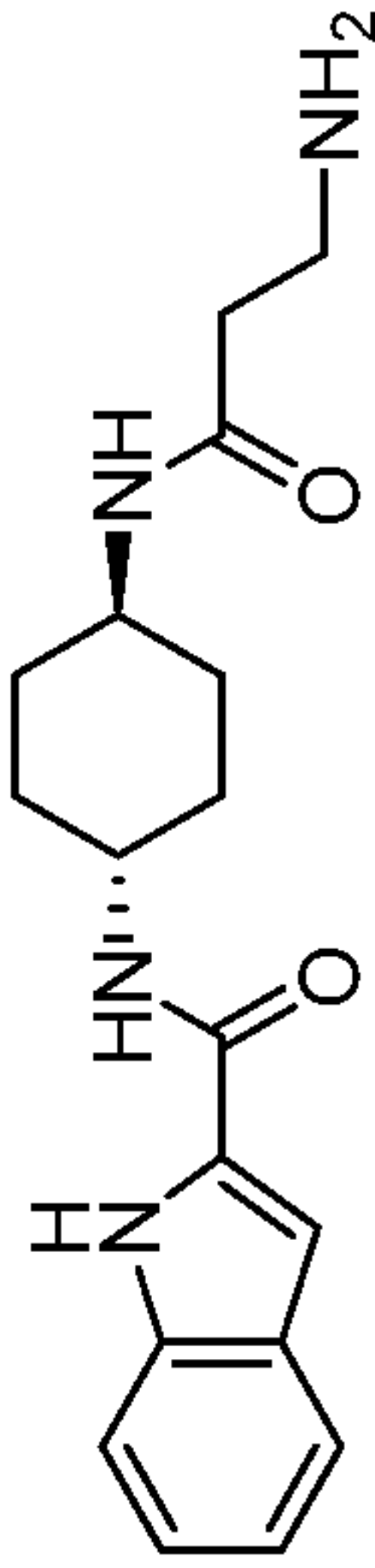
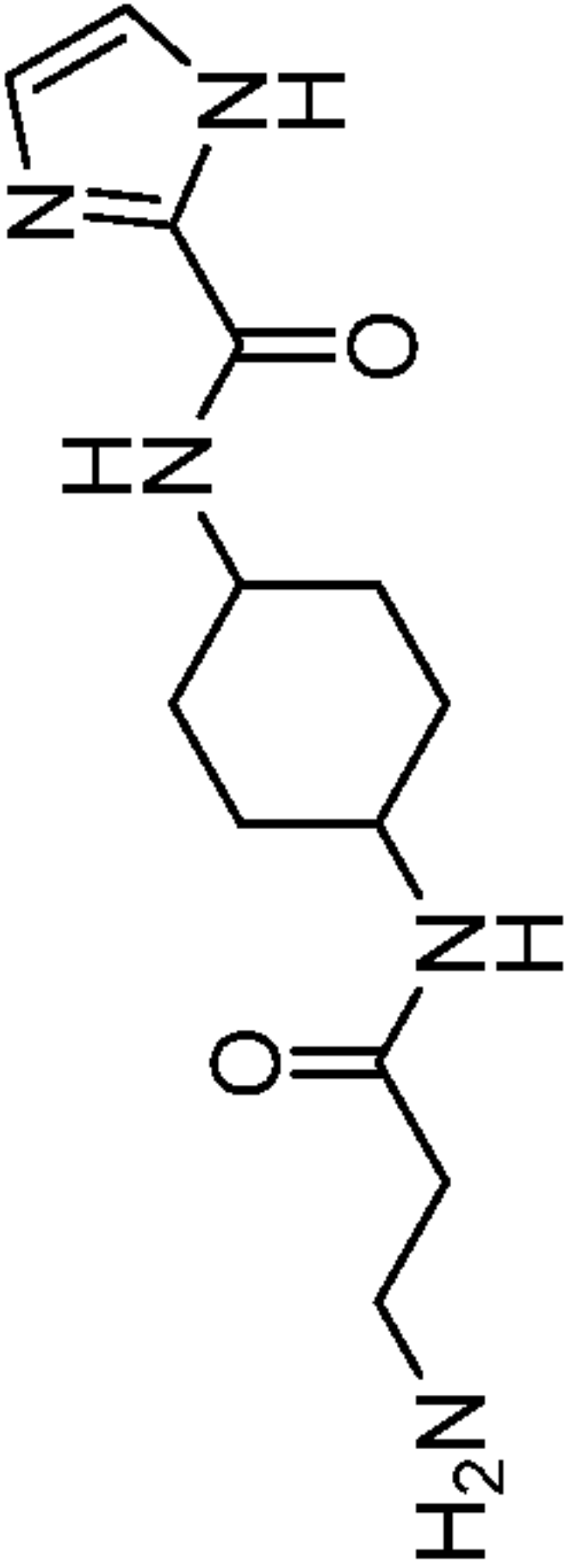
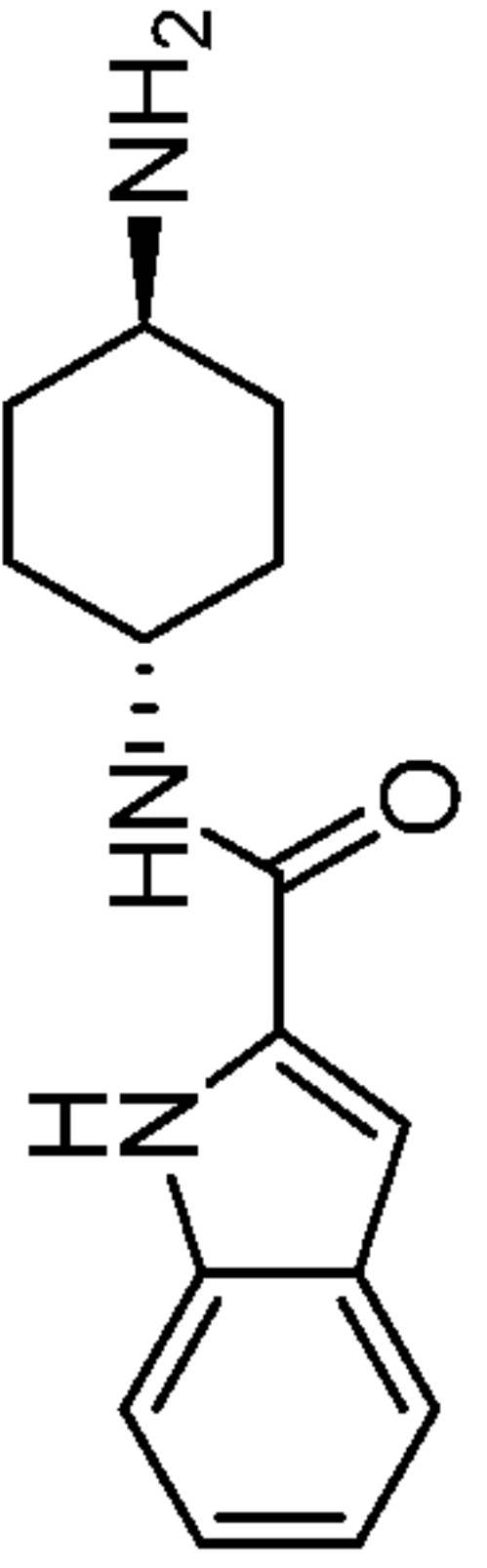
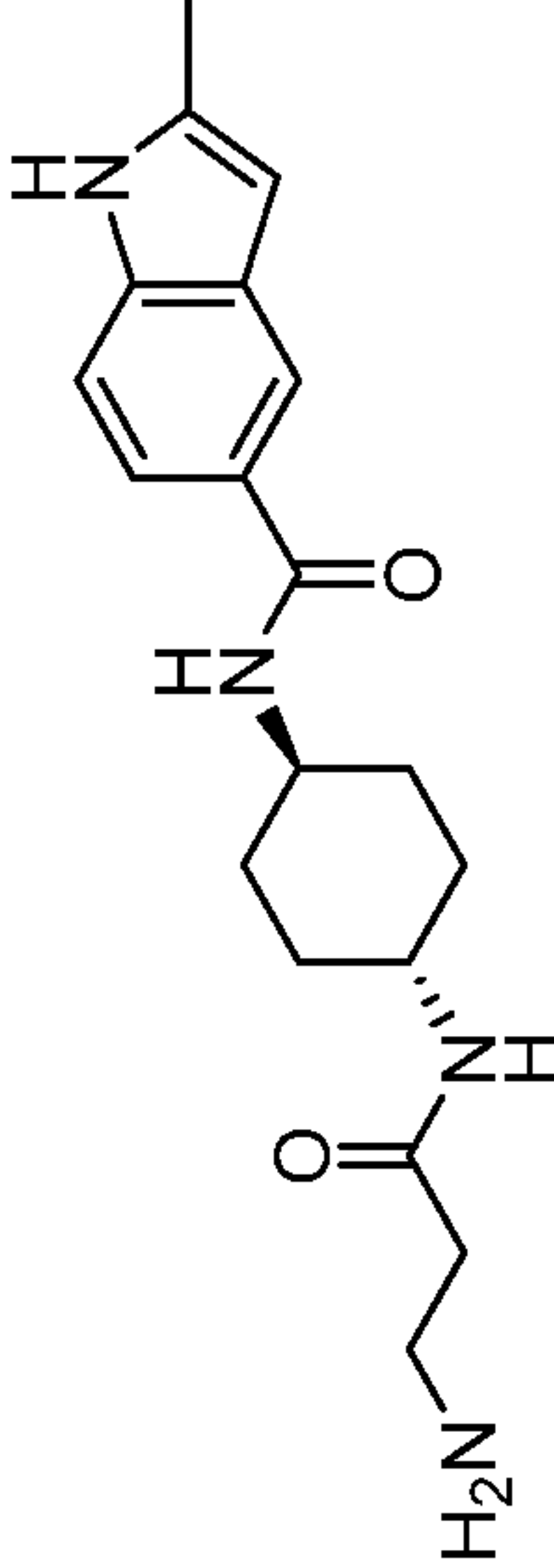
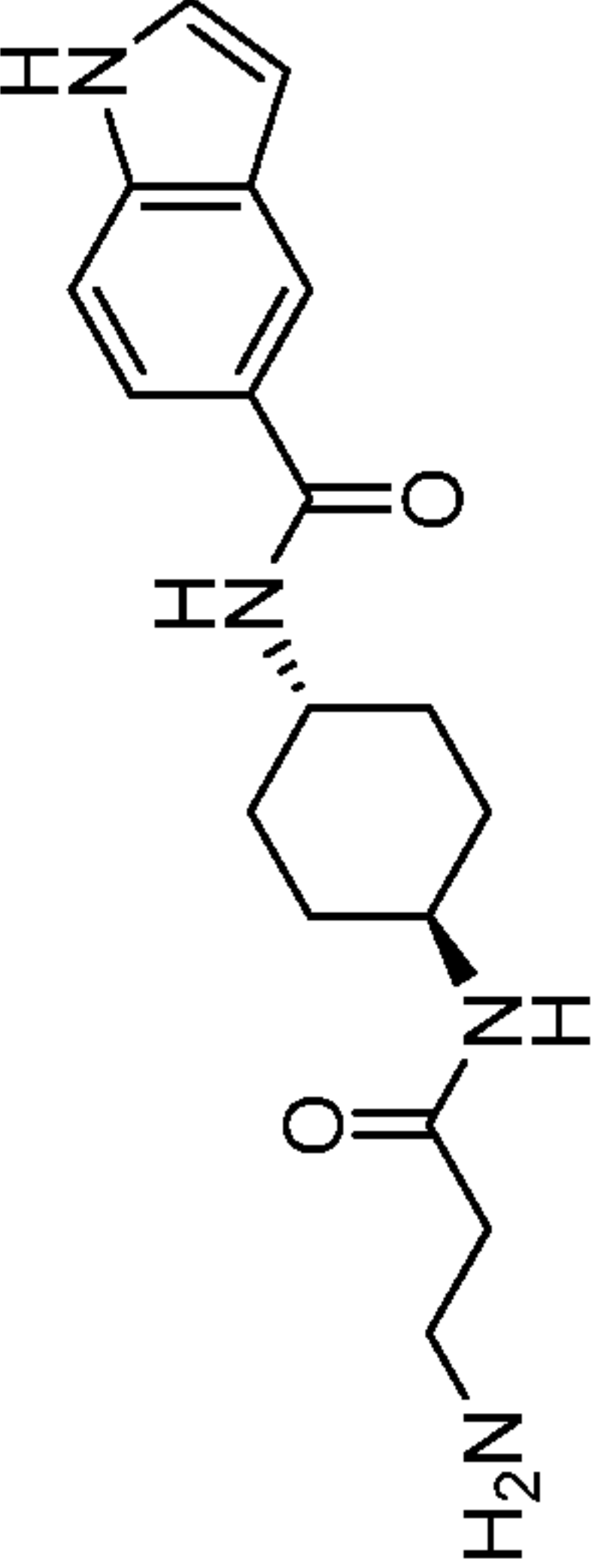
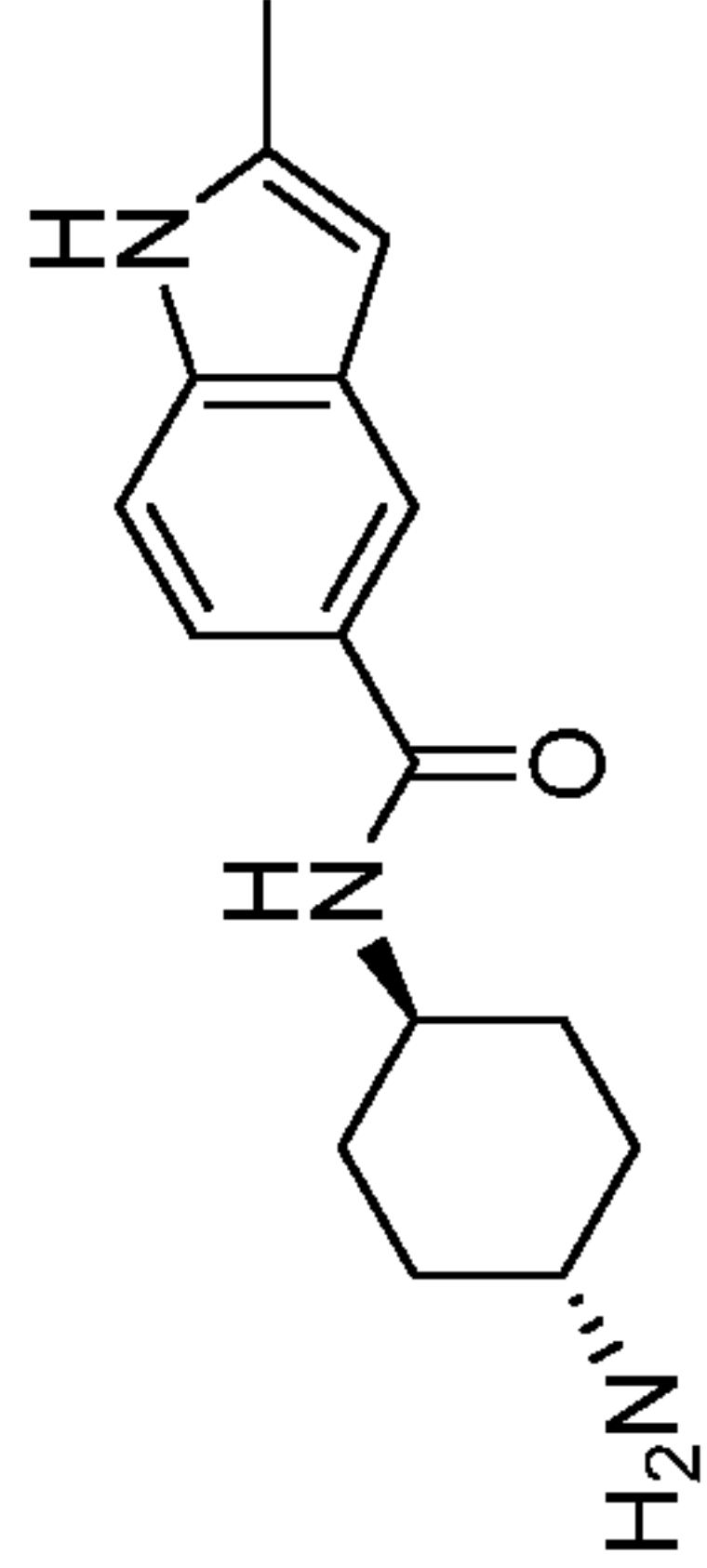
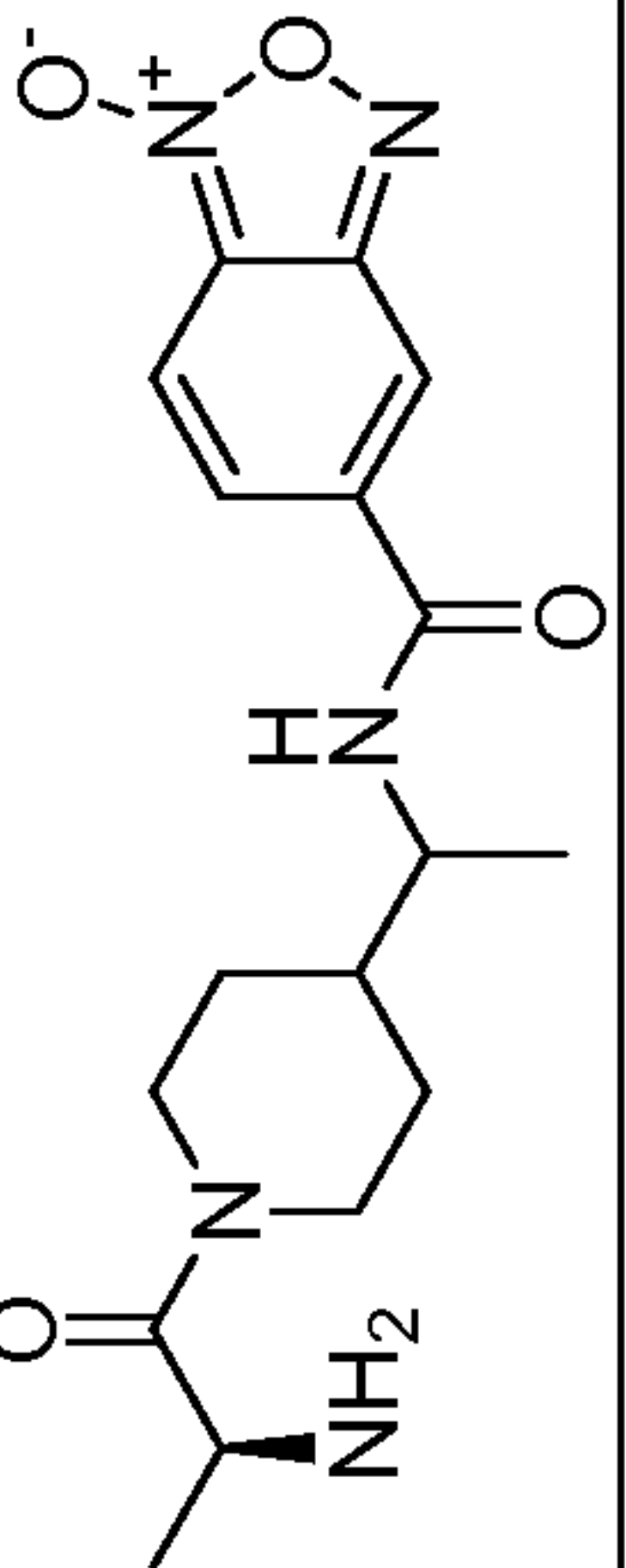
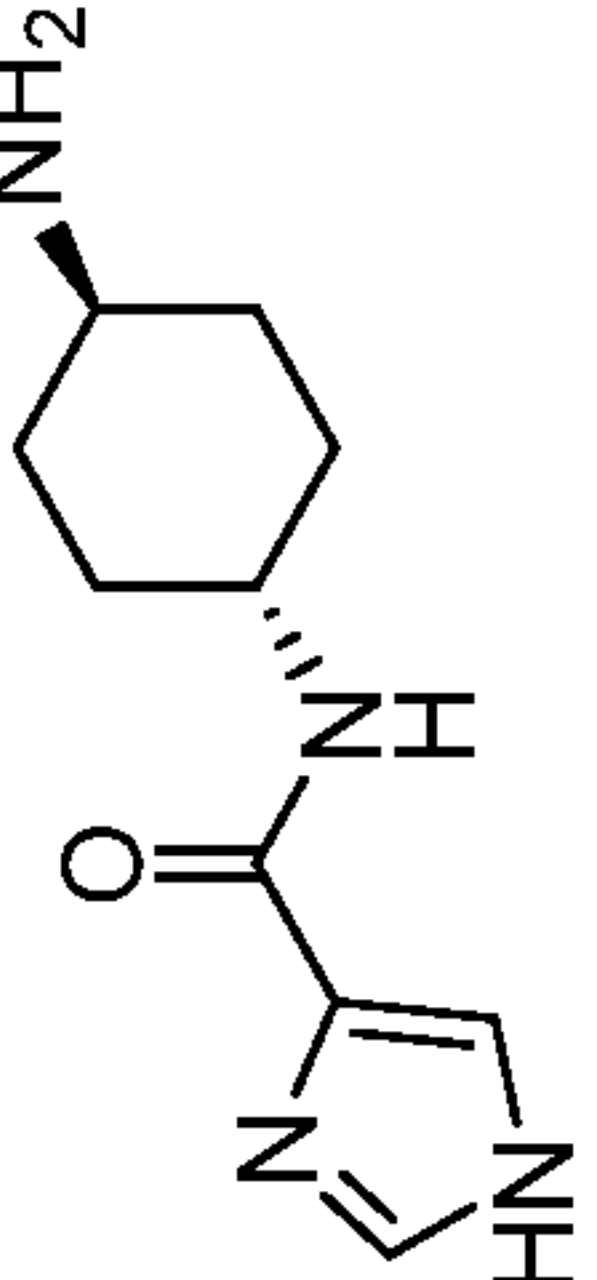
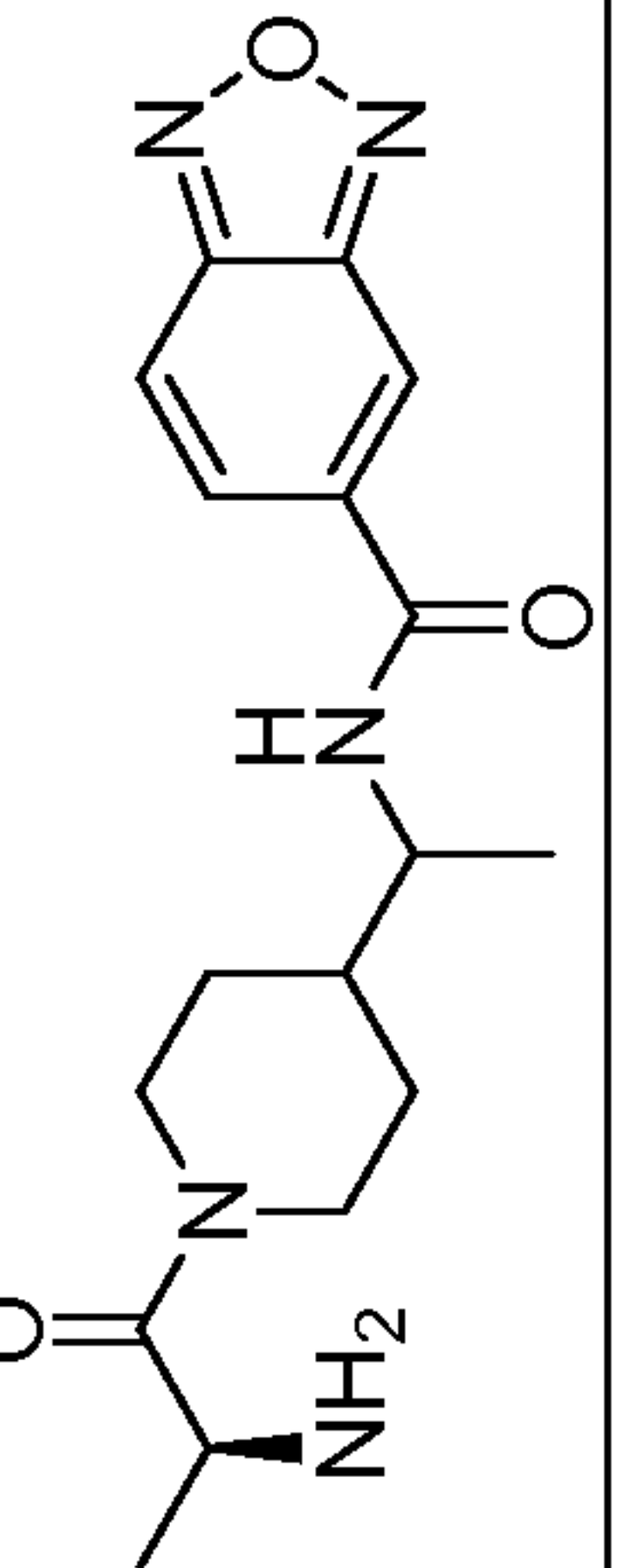
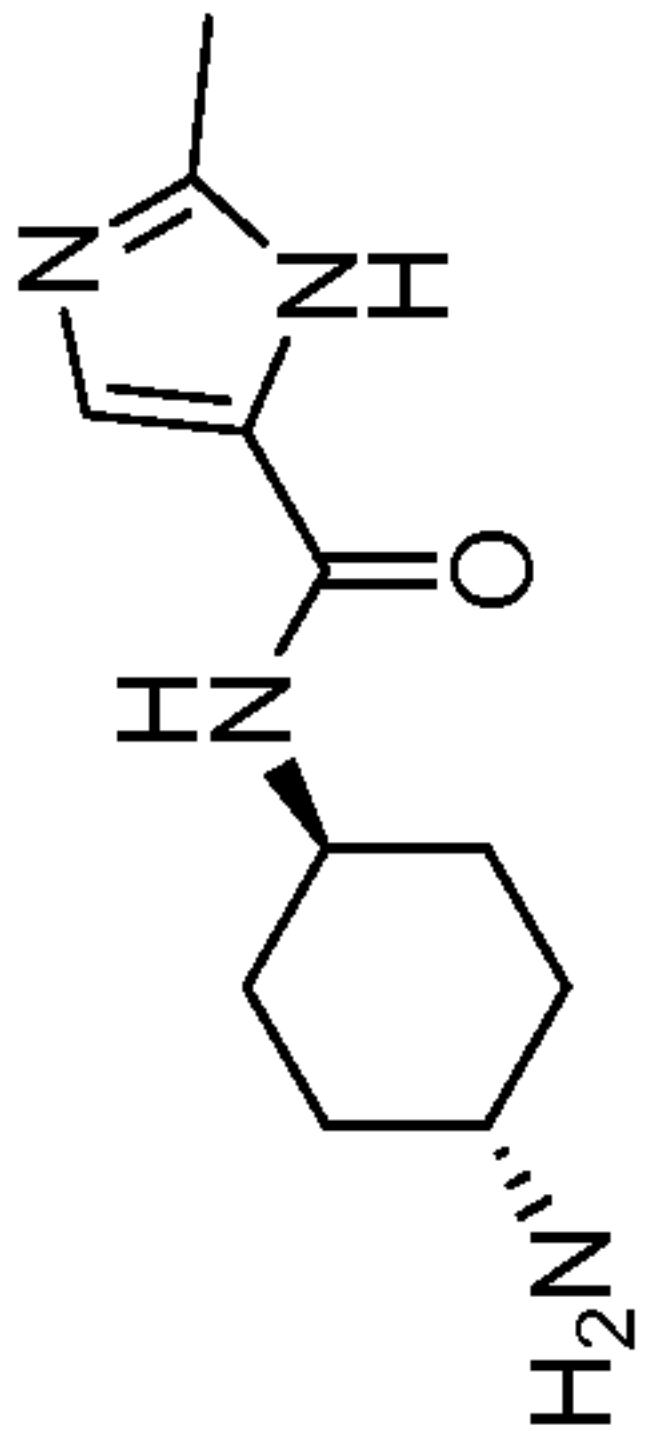
211		TFA	496		TFA
212		TFA	497		TFA
213		TFA	498		TFA
214		TFA	499		TFA
215		HCl	500		TFA

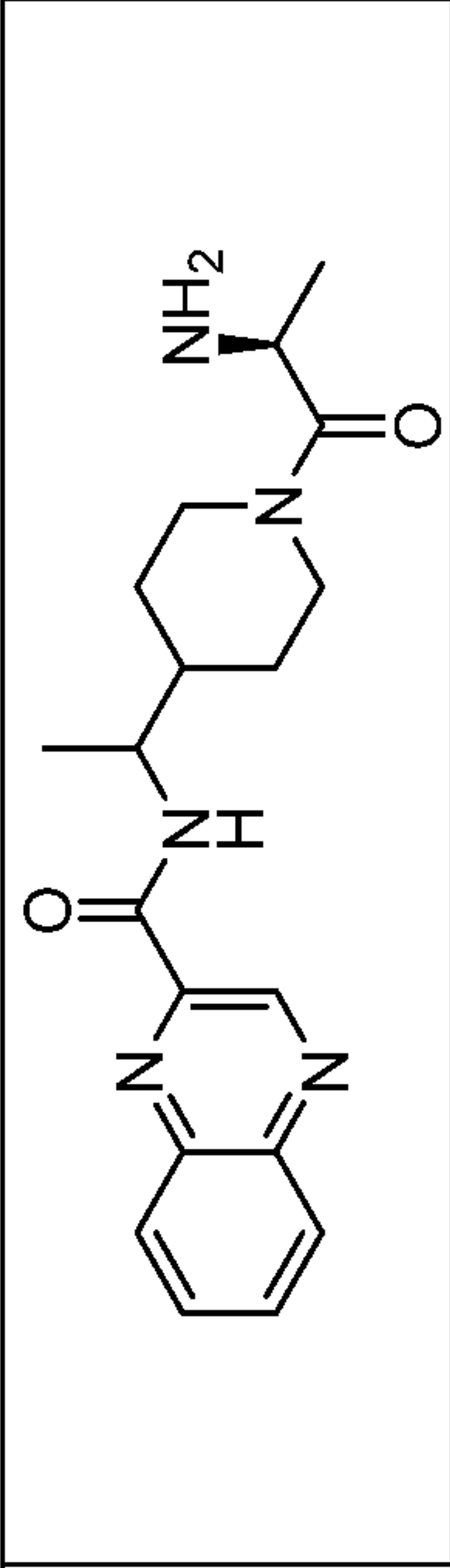
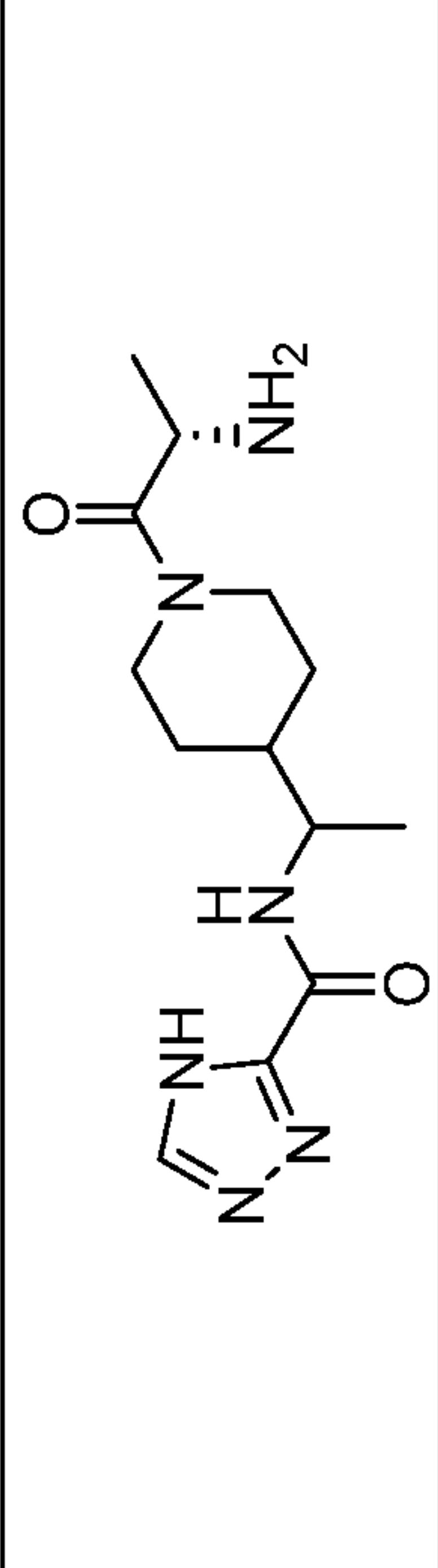
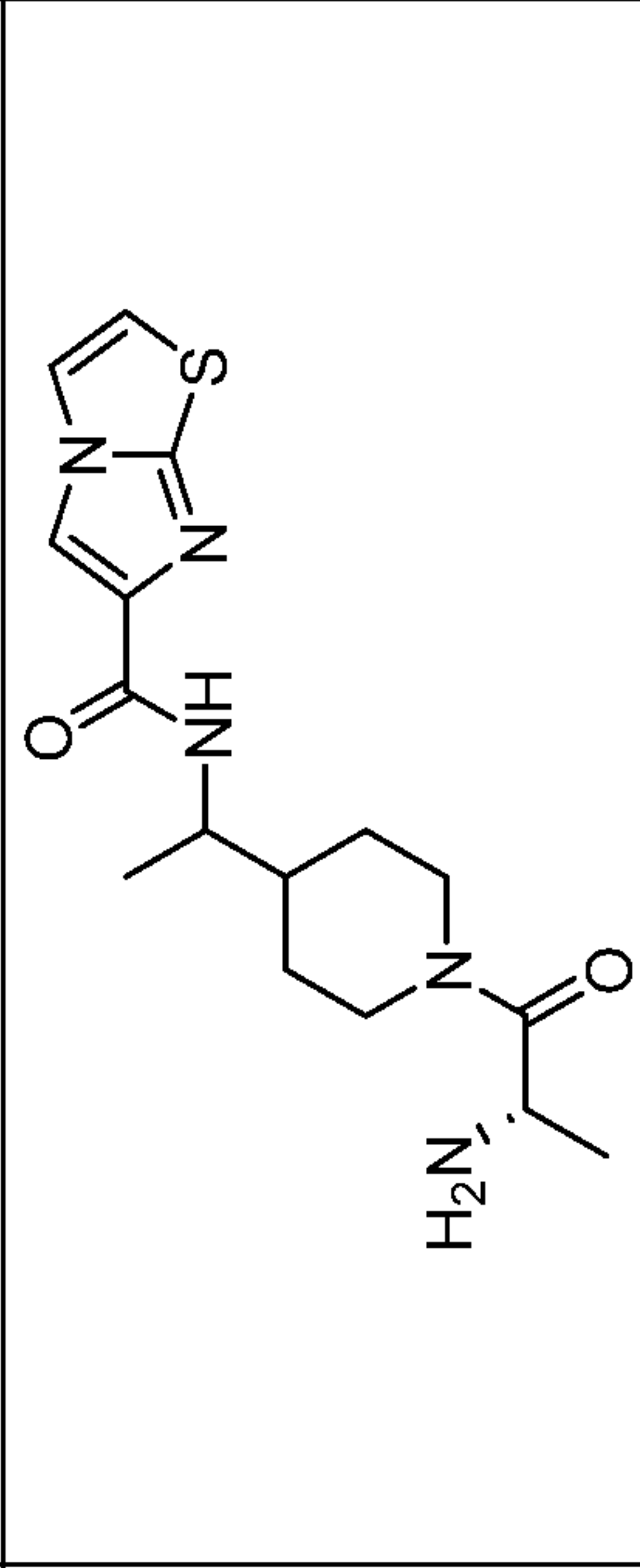
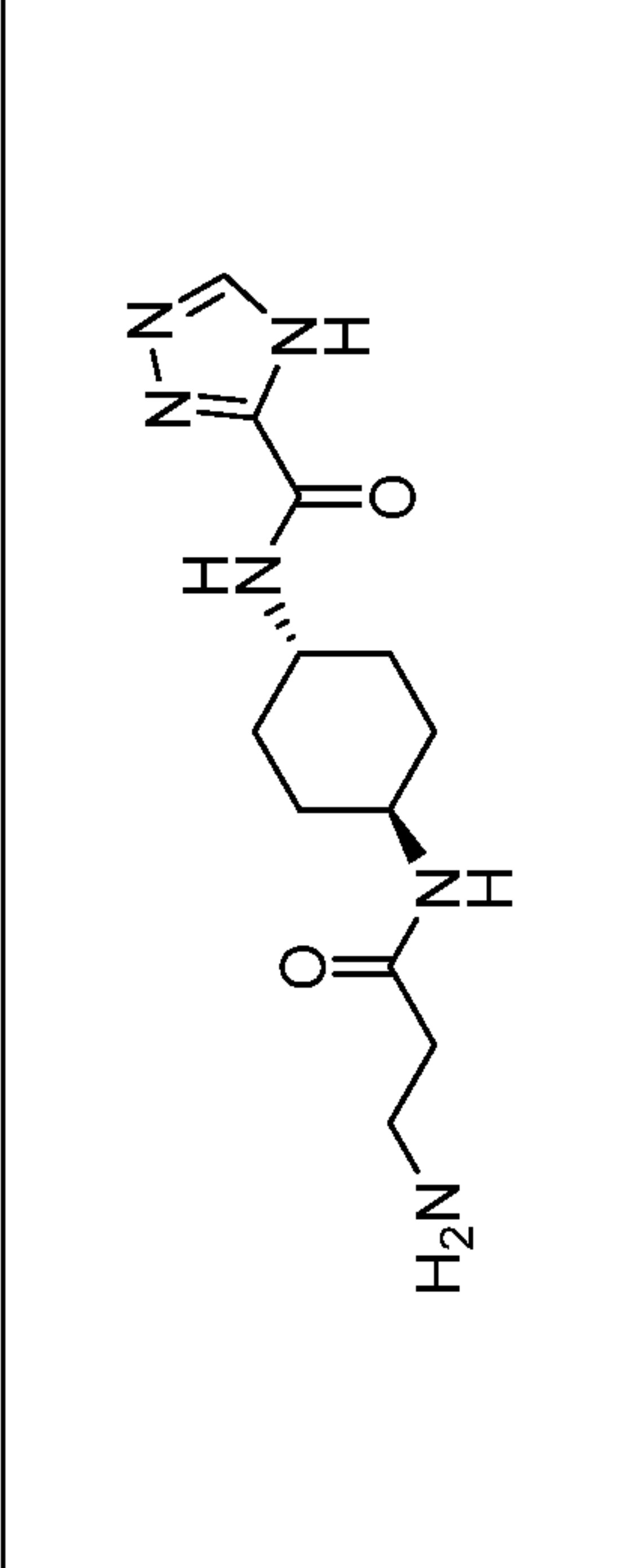
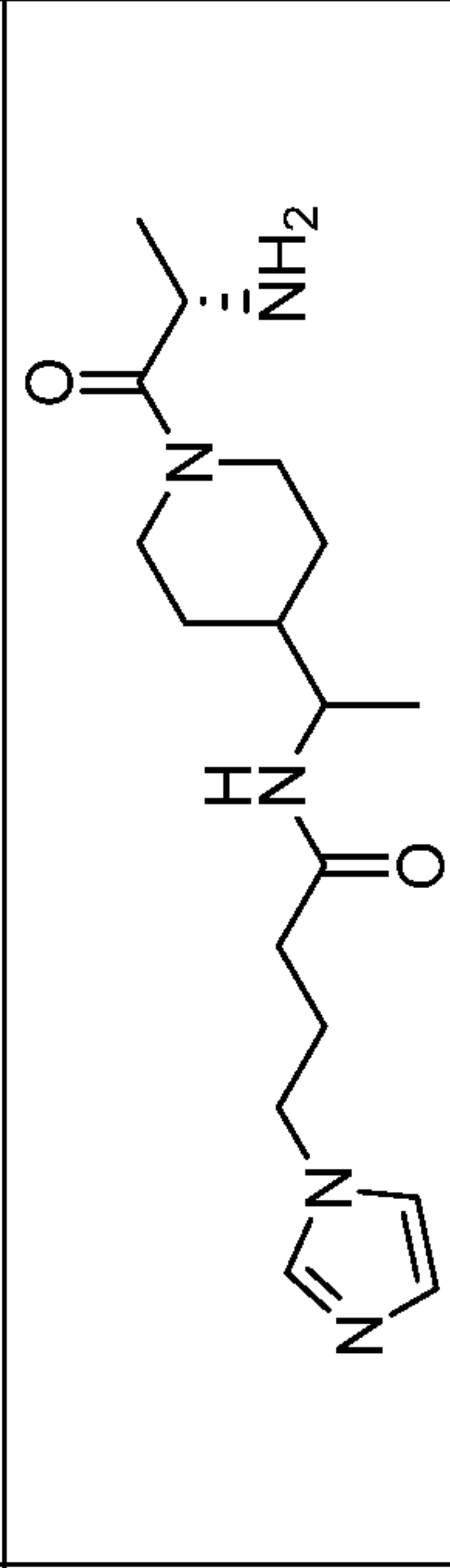
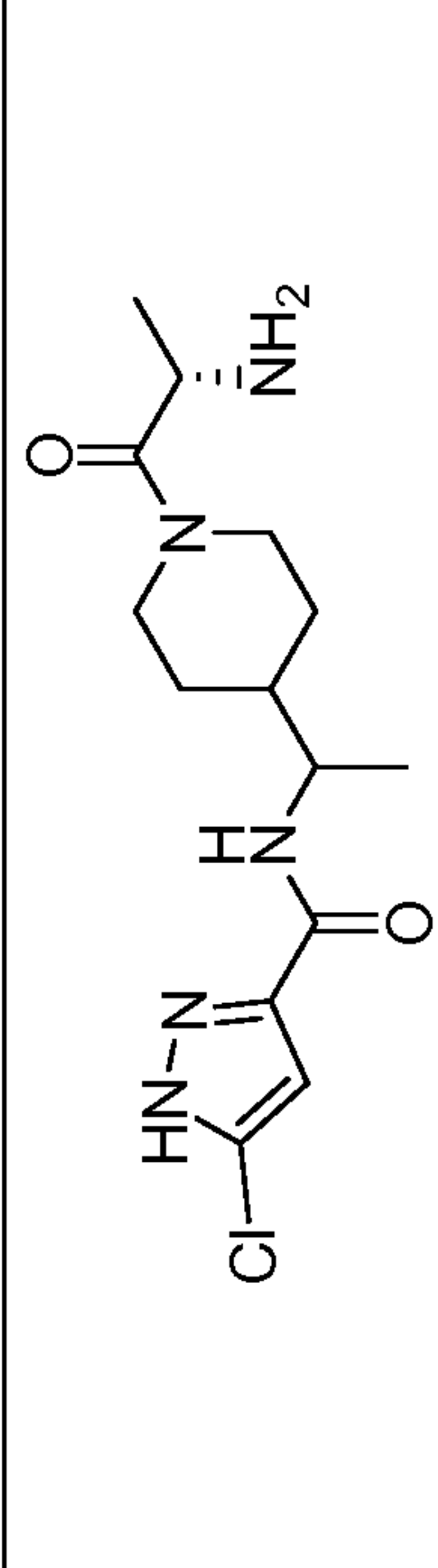
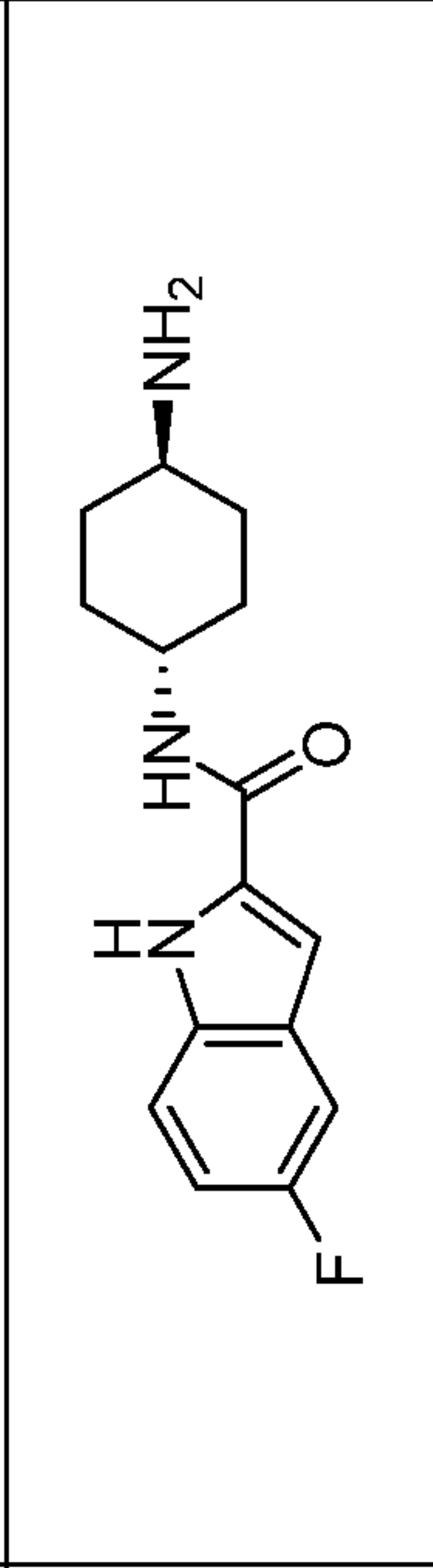
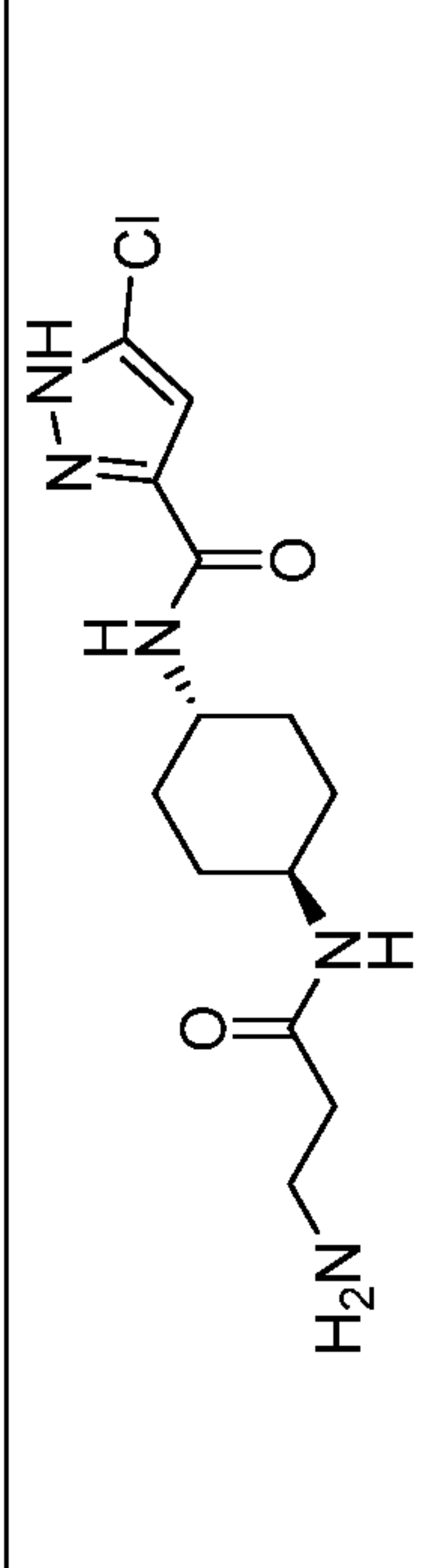
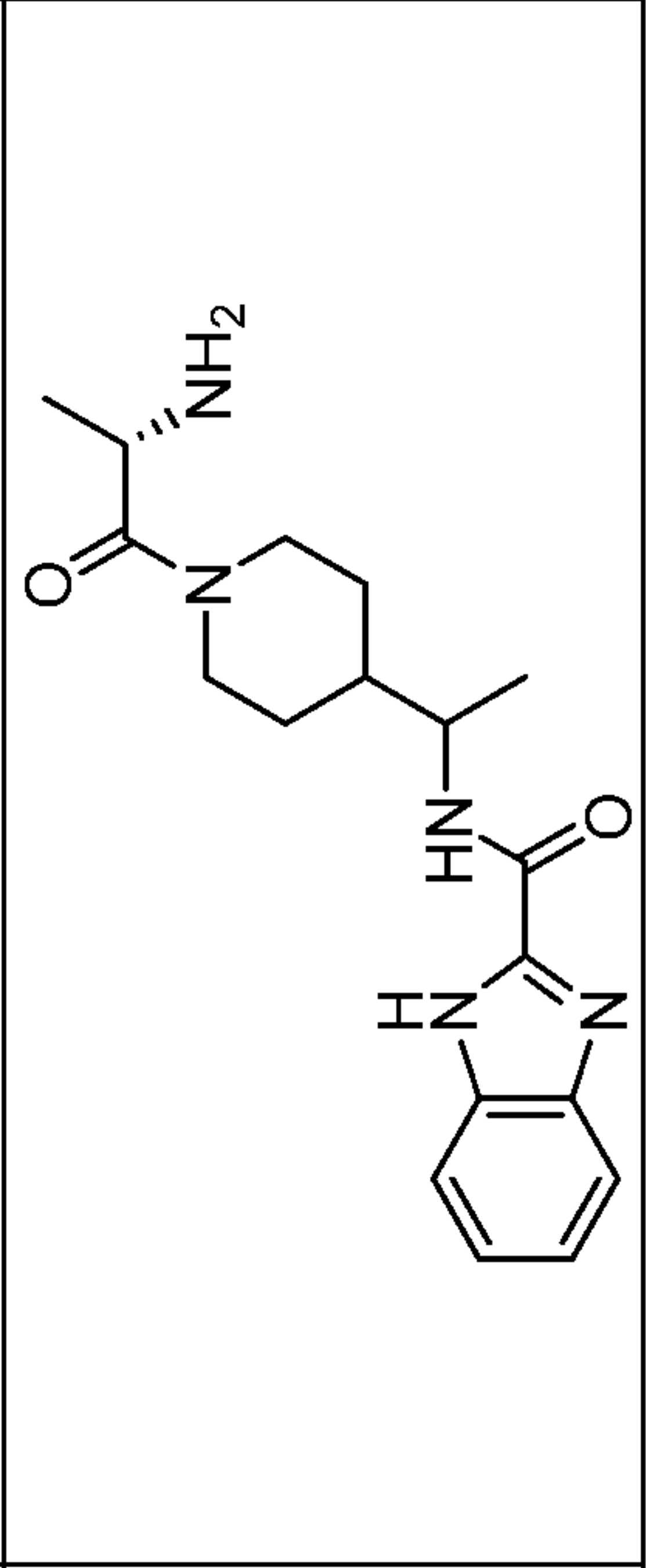
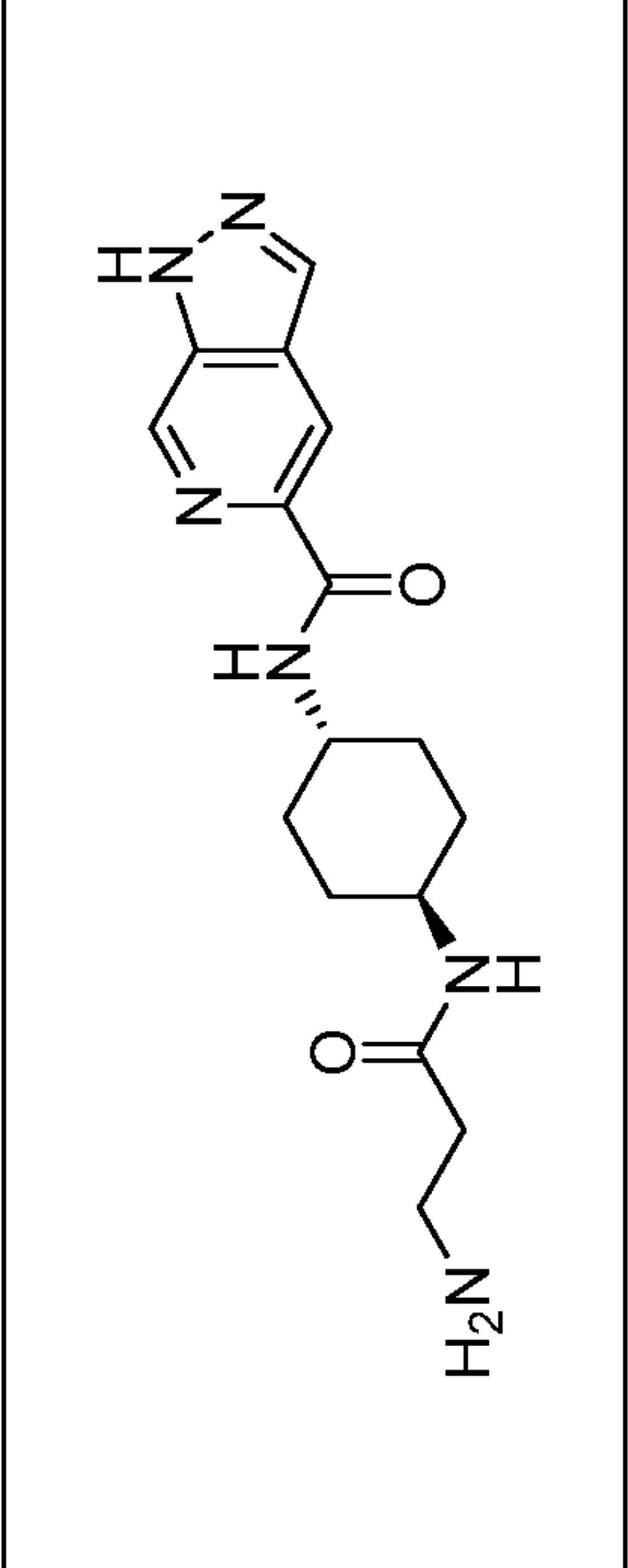
216		TFA	501		TFA
217		TFA	502		TFA
218		TFA	503		TFA
219		TFA	504		TFA

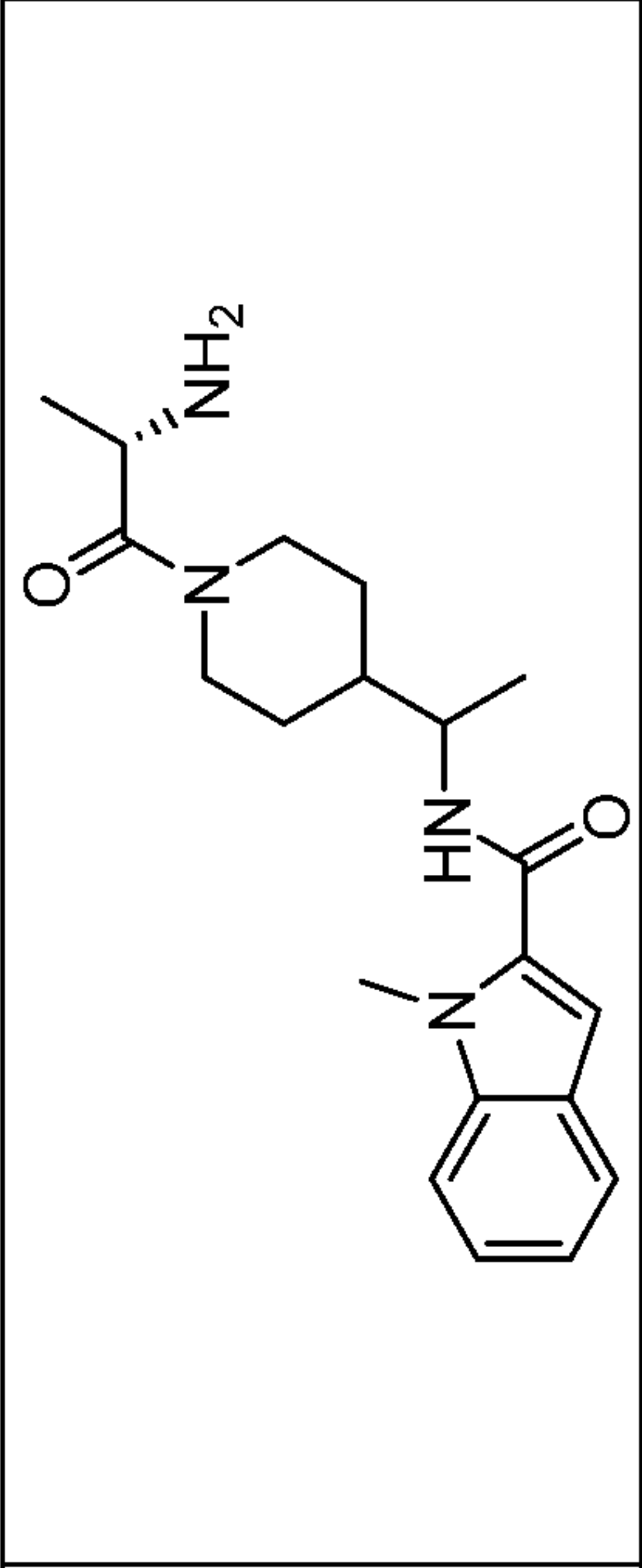
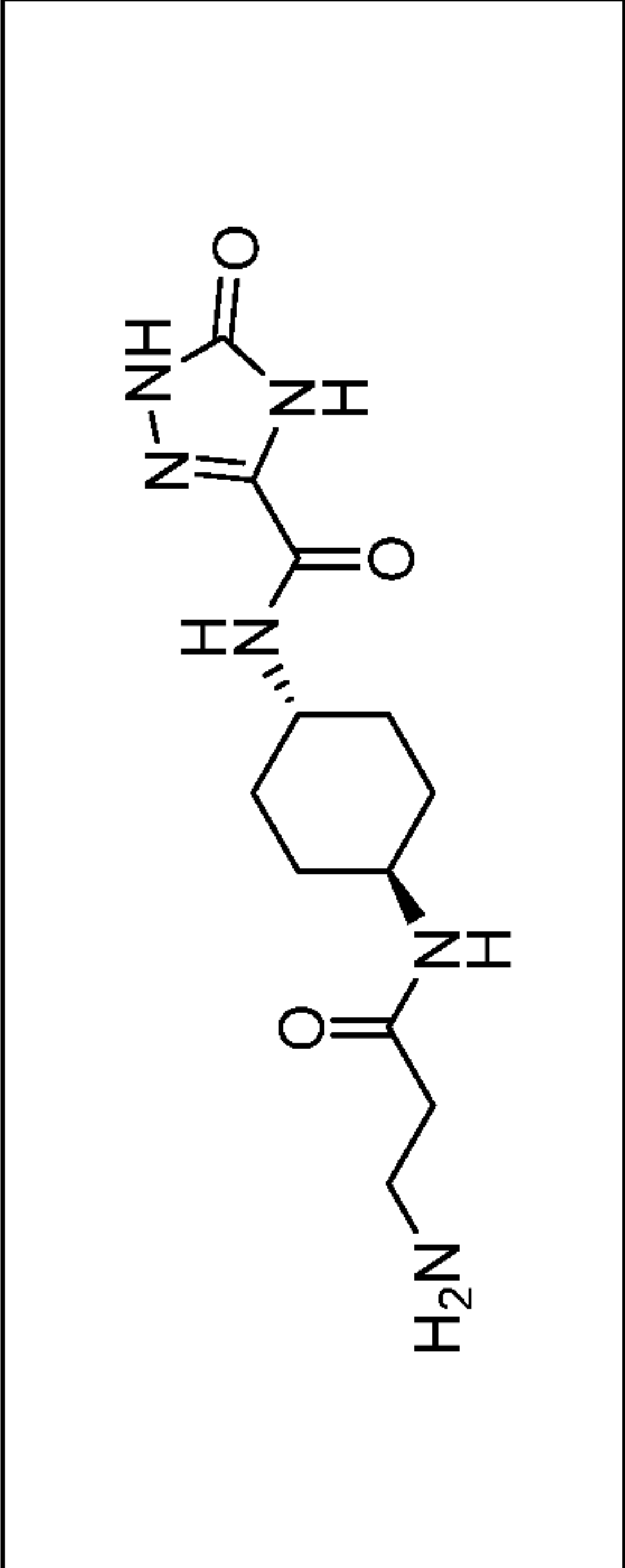
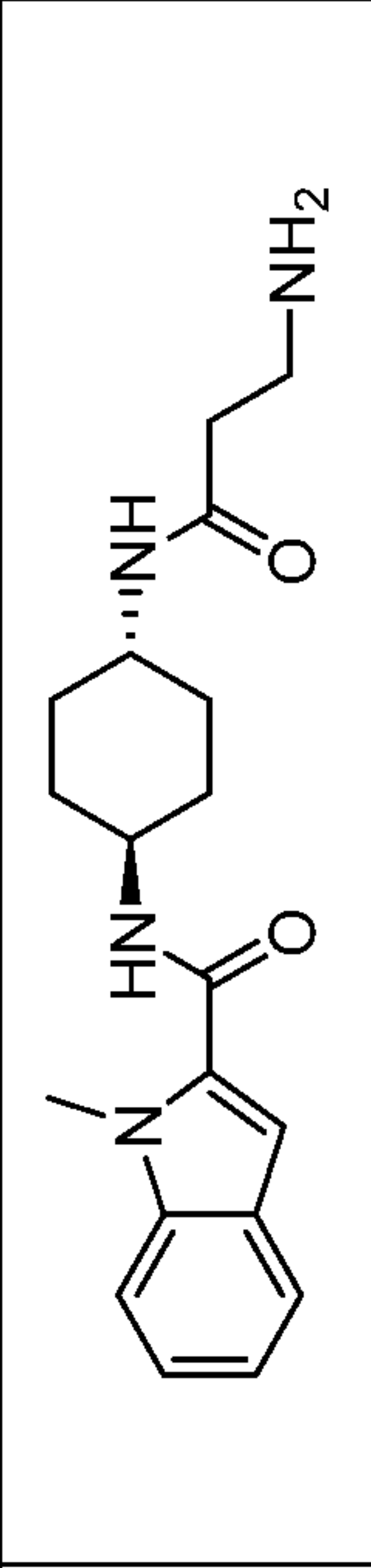
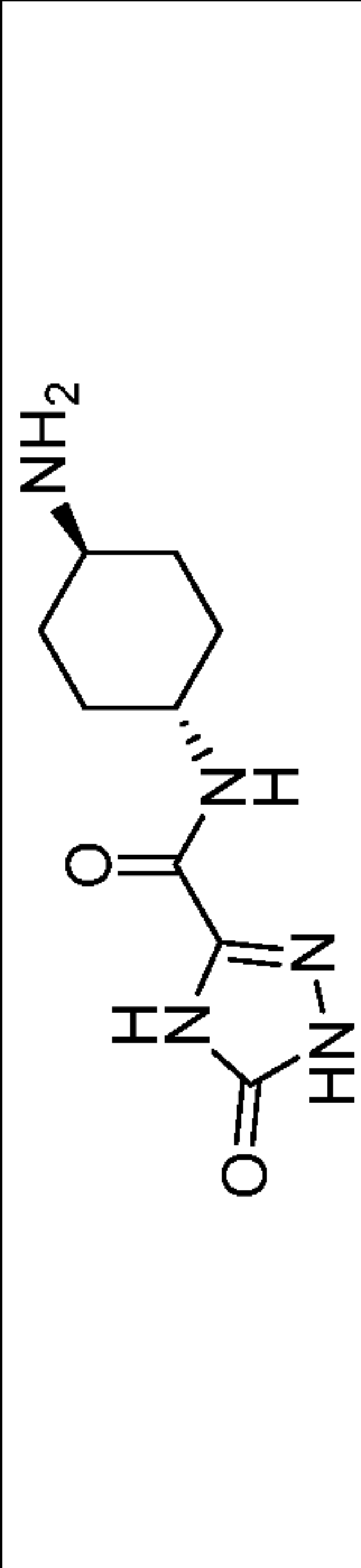
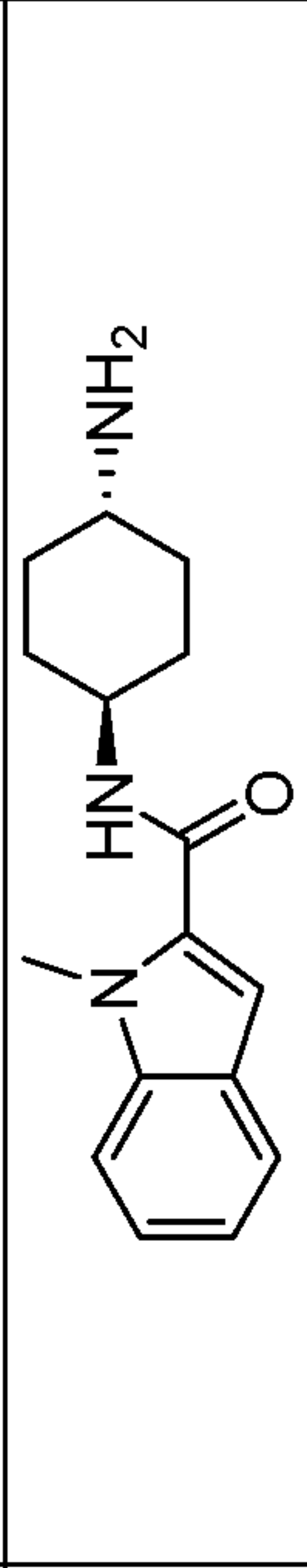
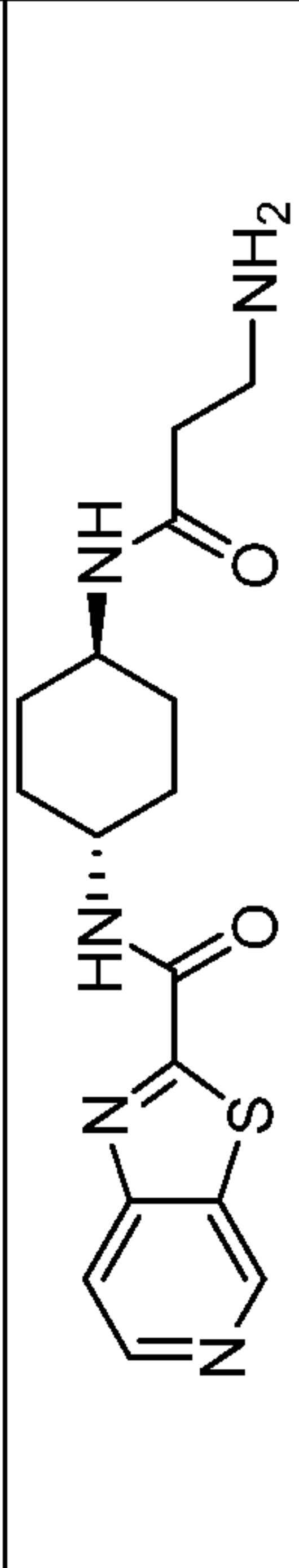
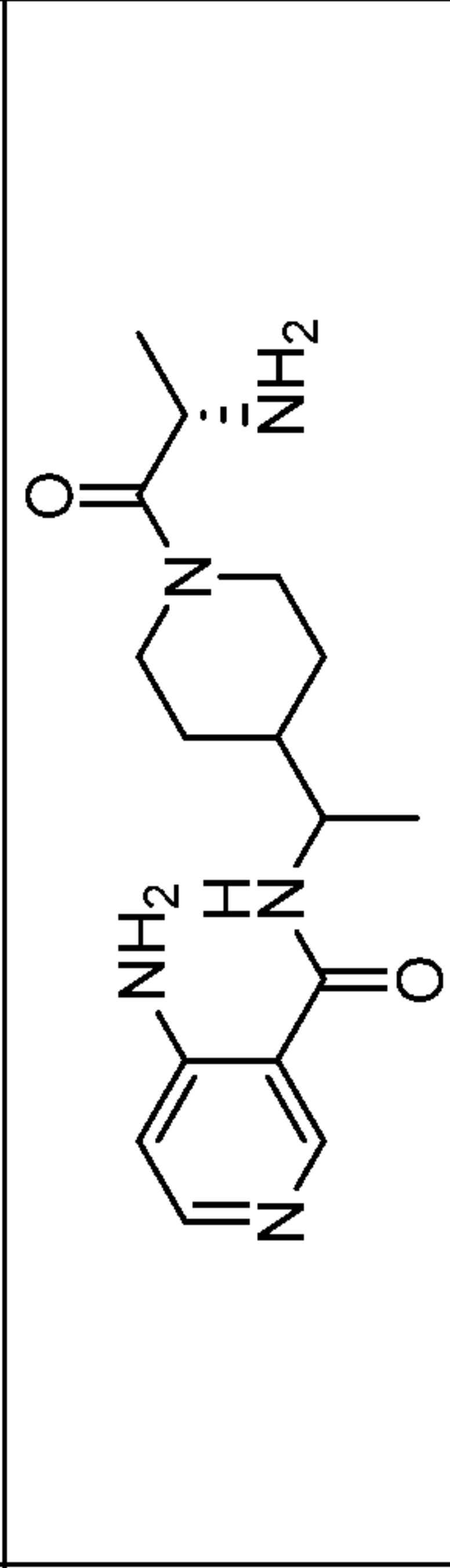
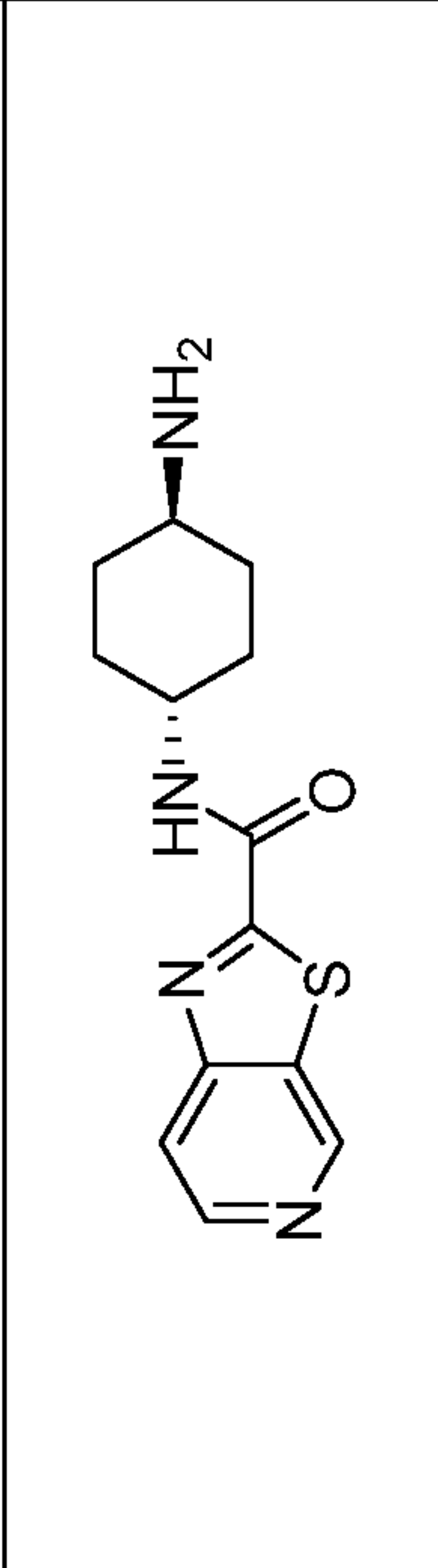
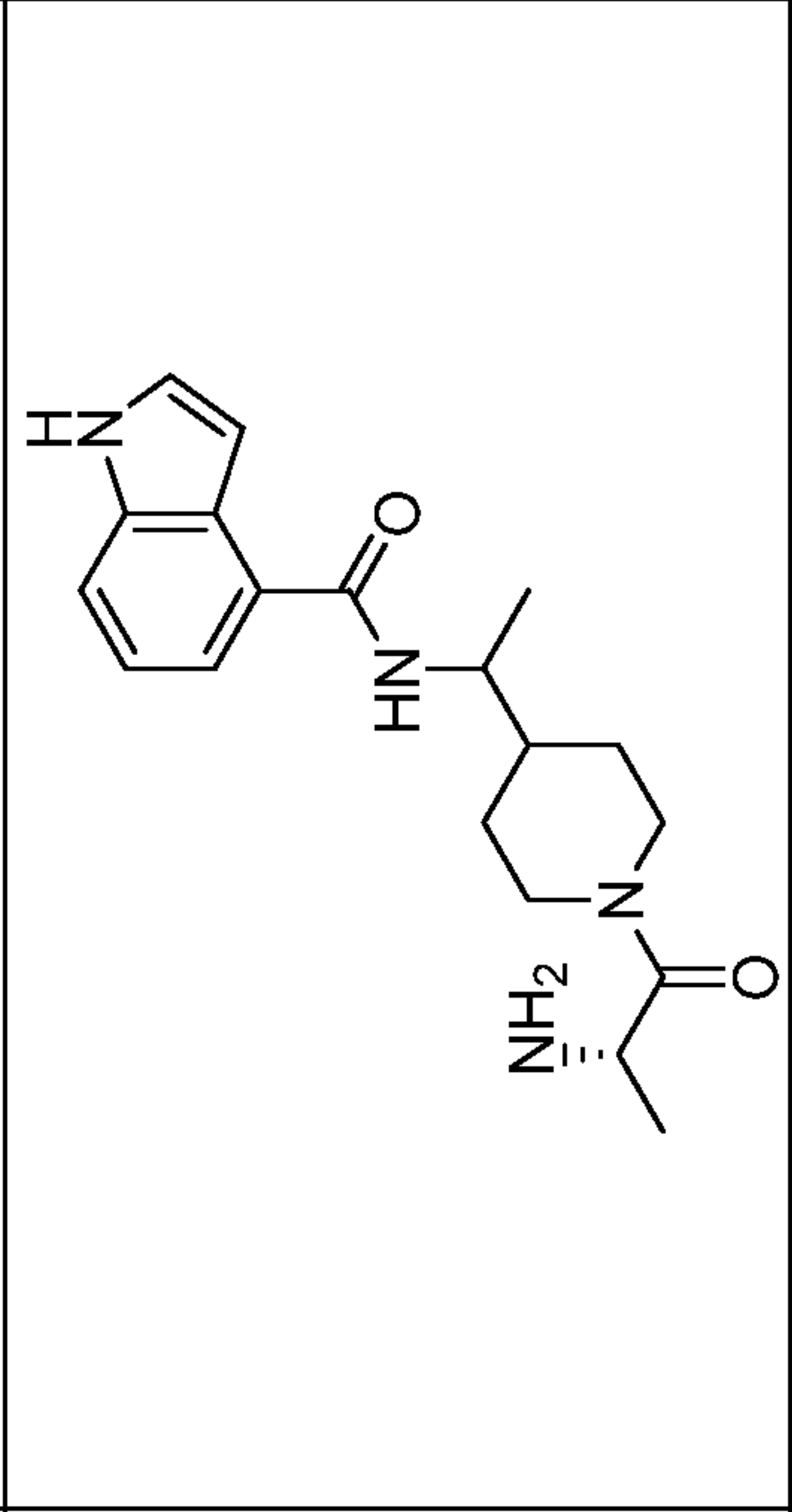
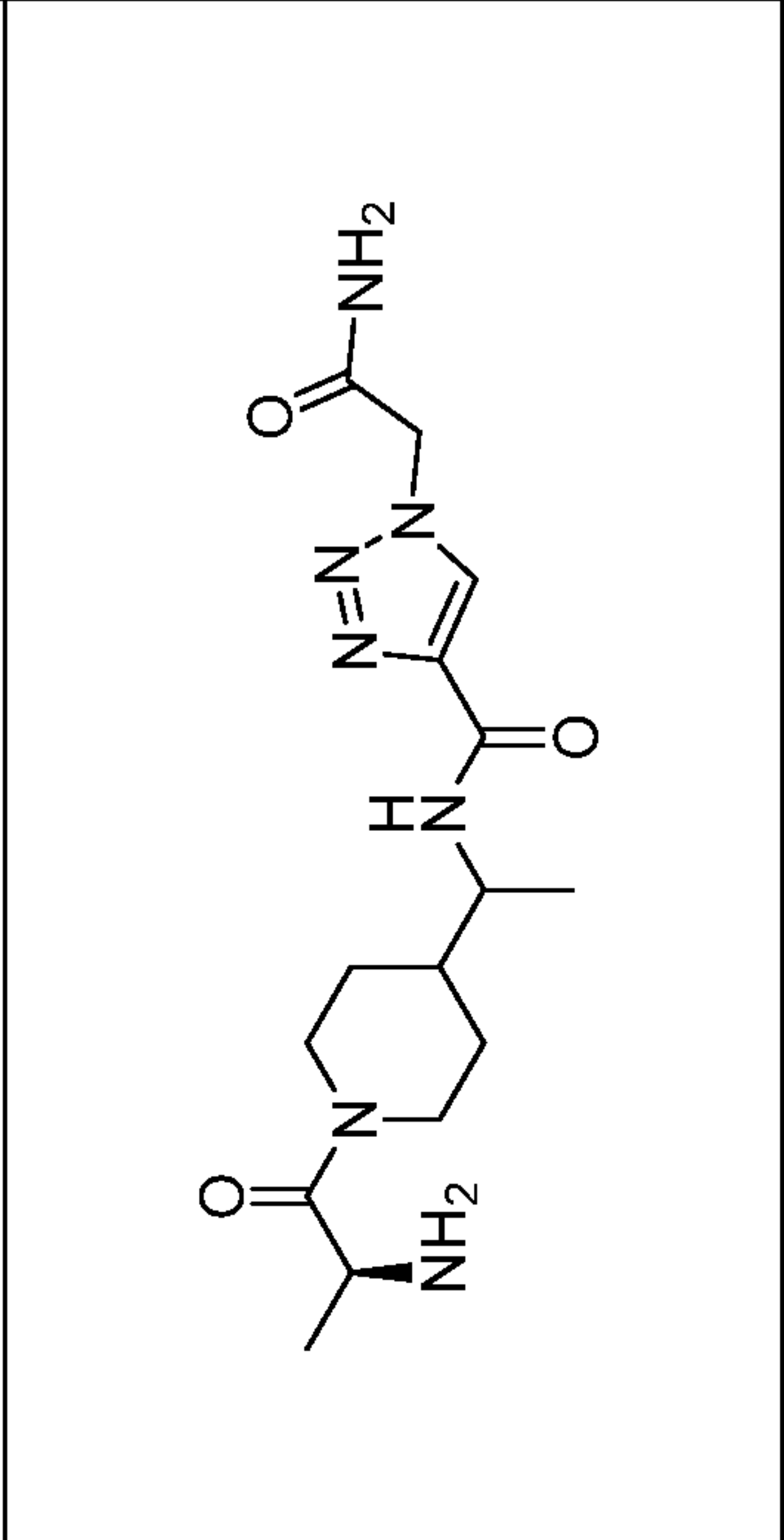
220		TFA	505		TFA
221		TFA	506		TFA
222		TFA	507		TFA

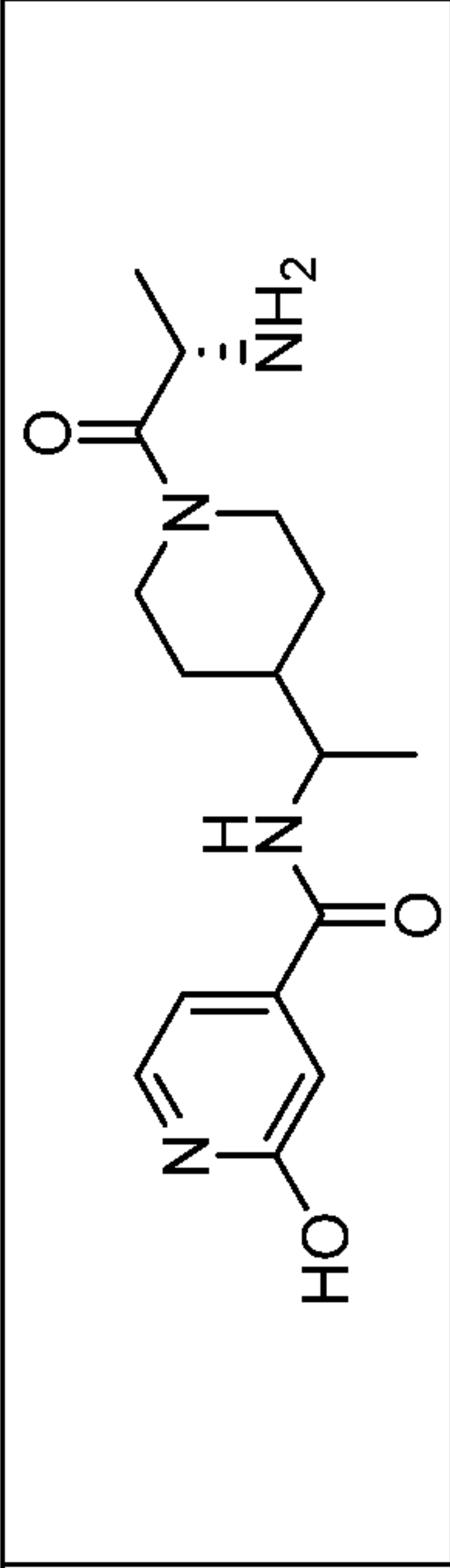
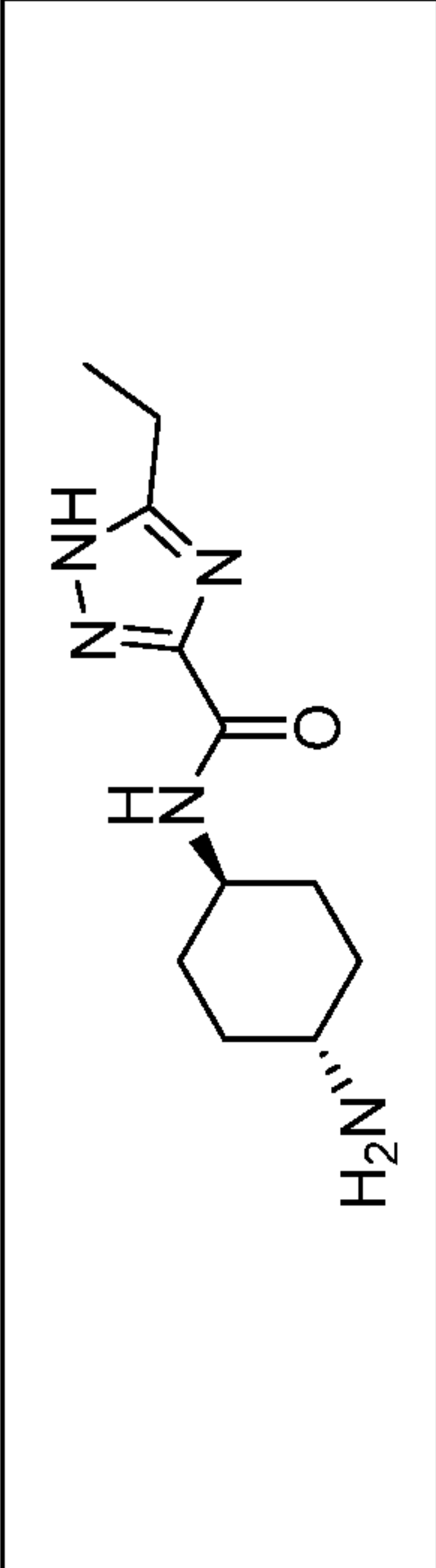
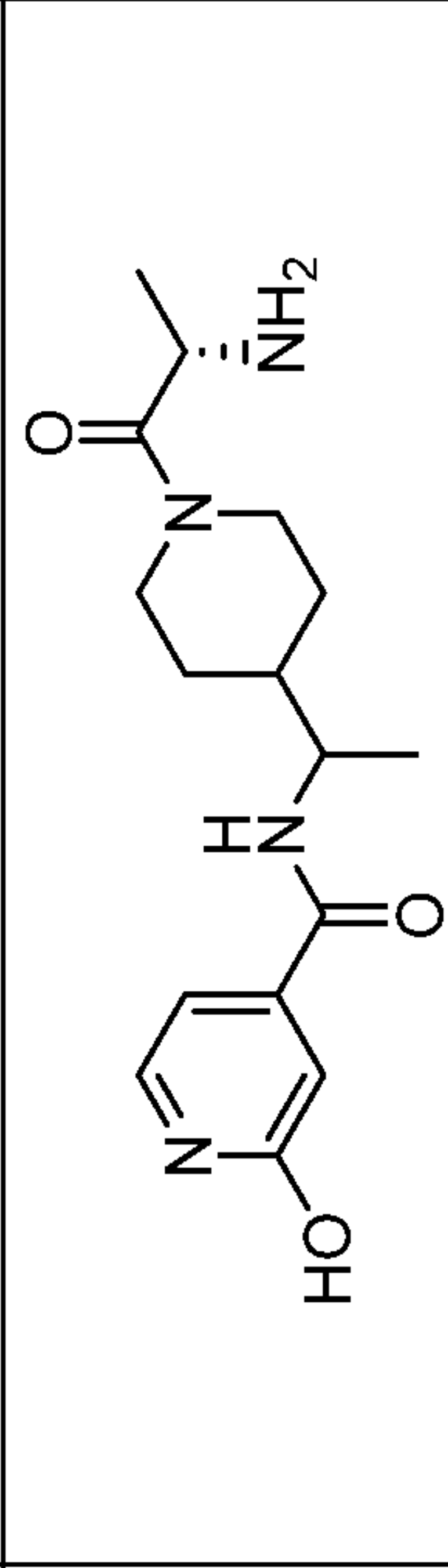
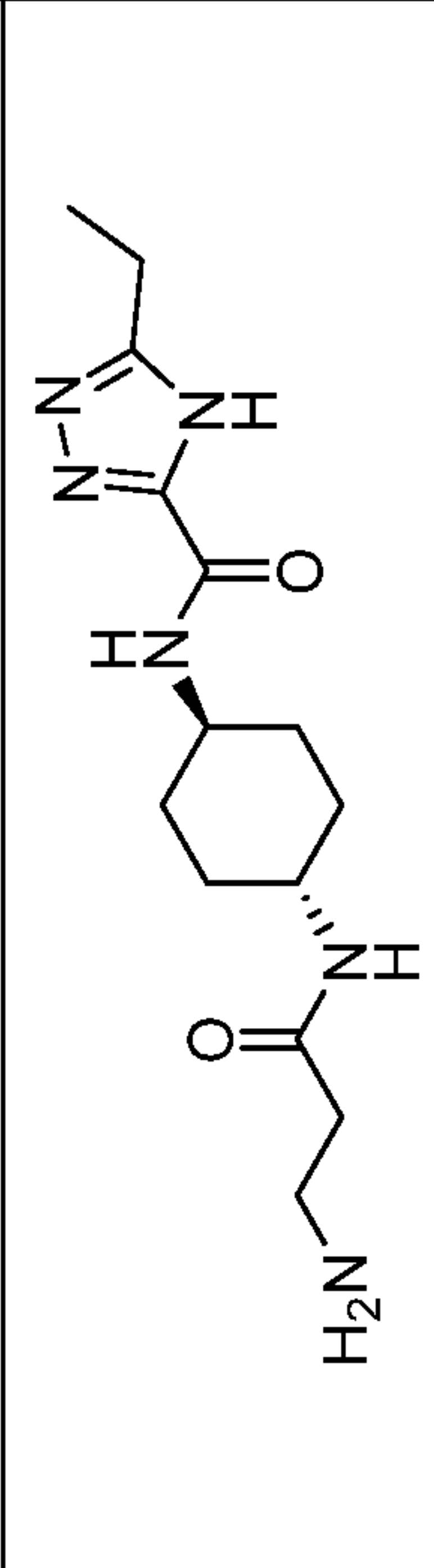
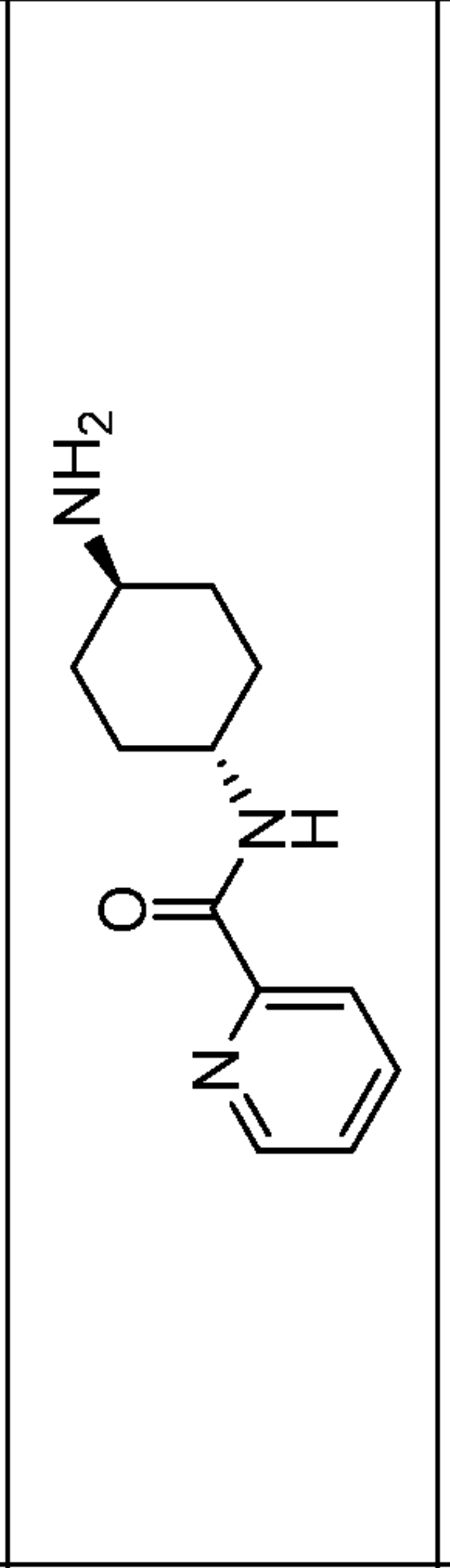
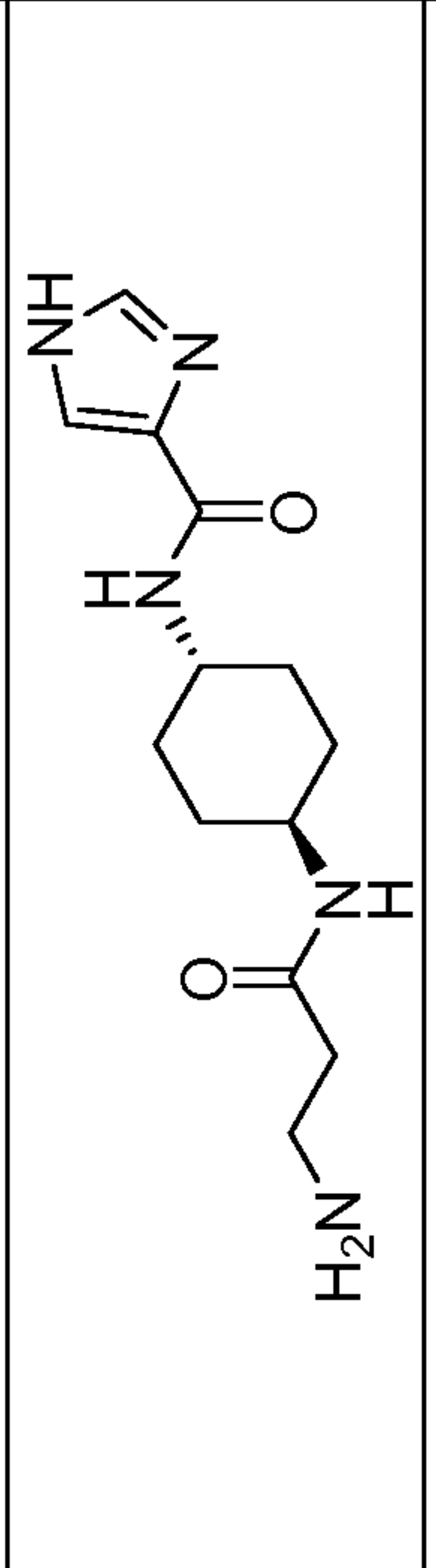
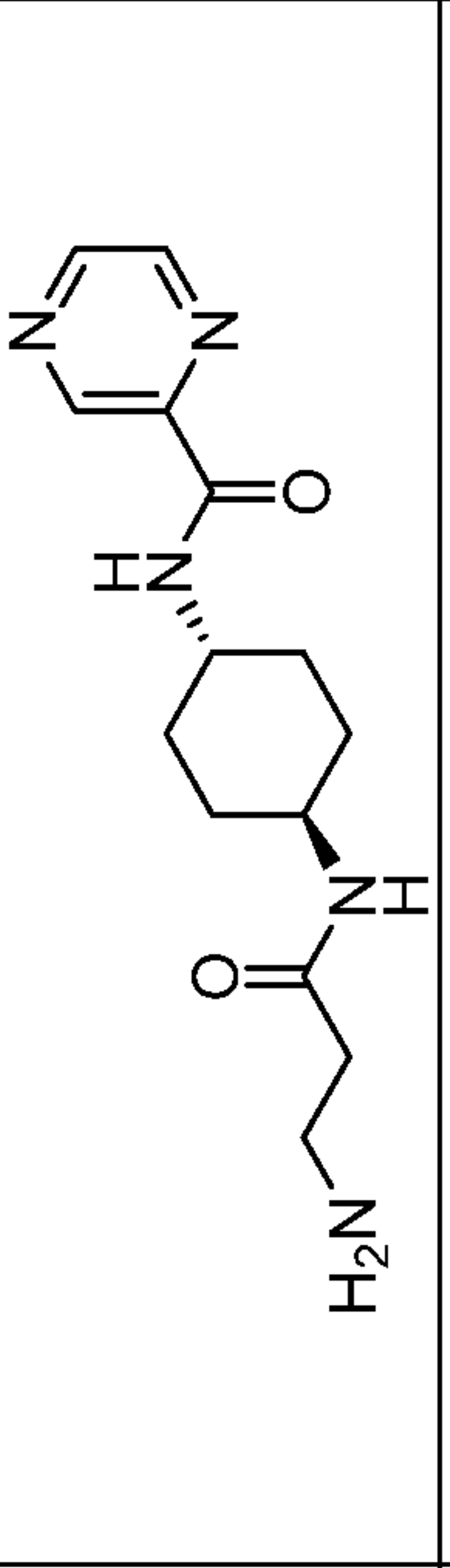
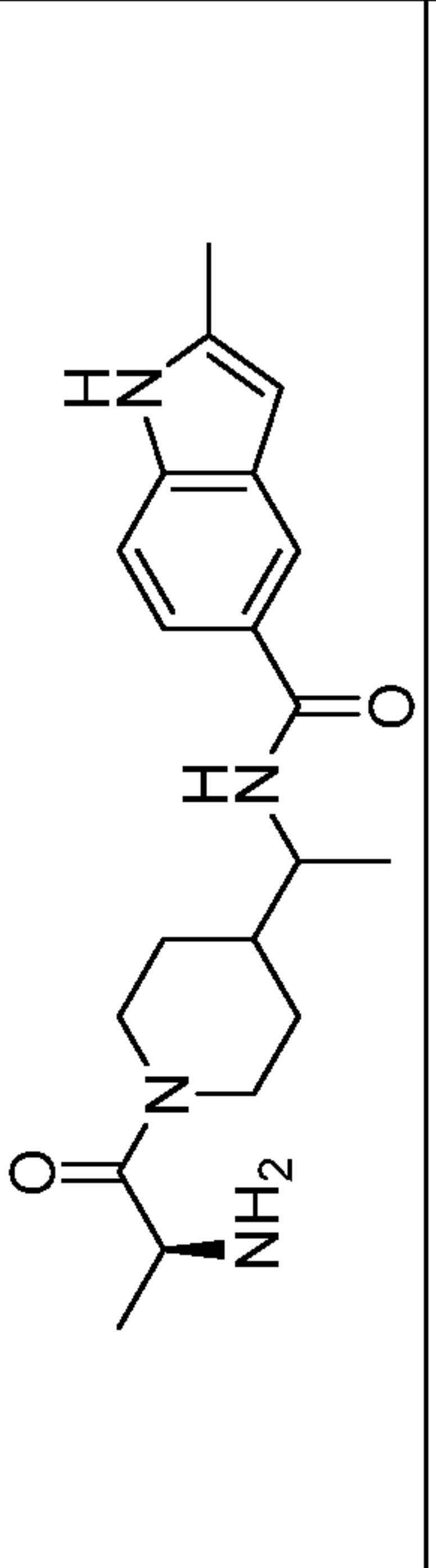
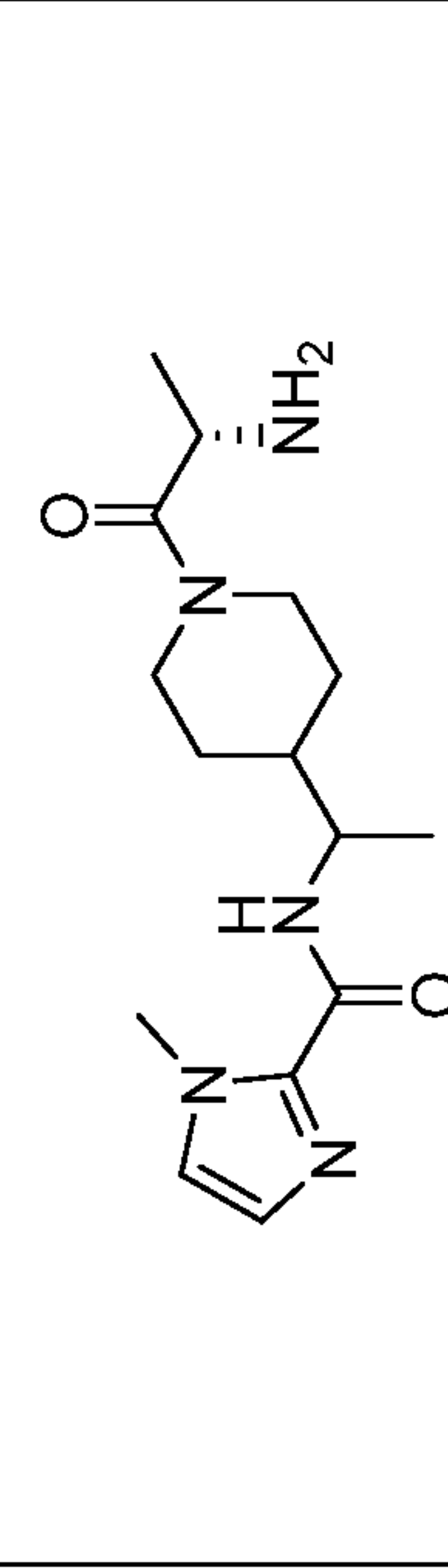
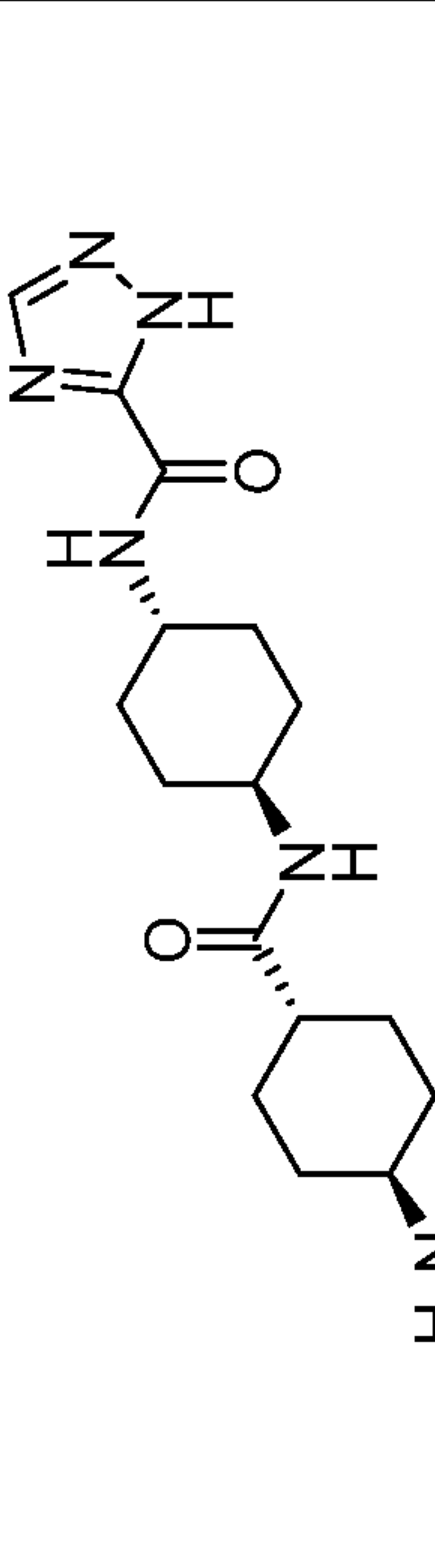
223		TFA	508		TFA
224		TFA	509		TFA
225		TFA	510		TFA
226		TFA	511		HCl
227		TFA	512		TFA

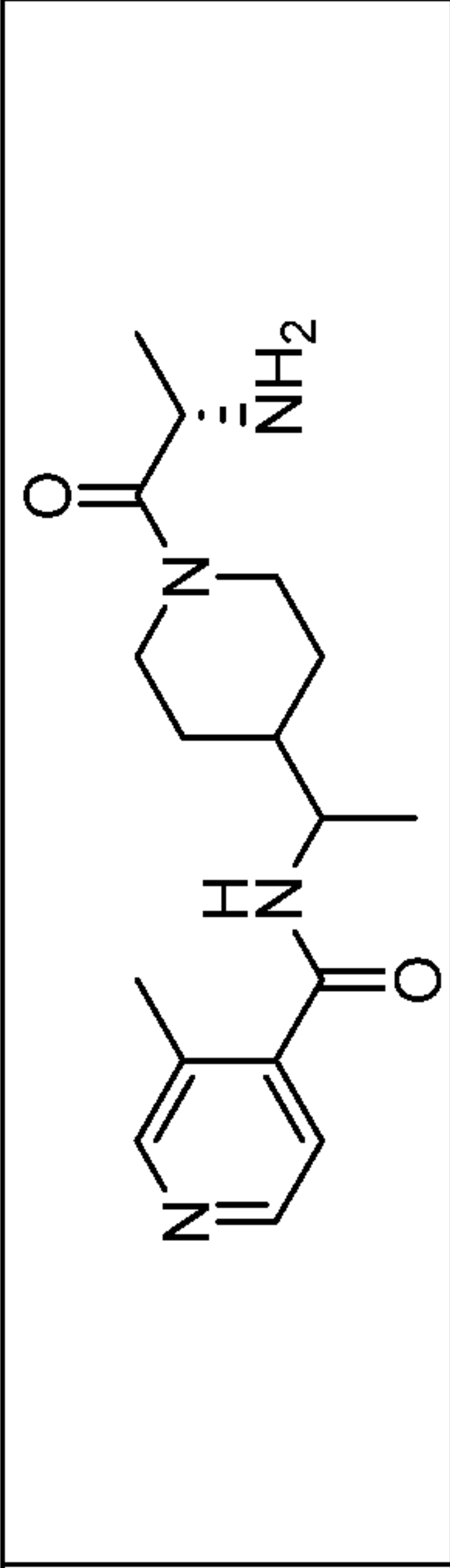
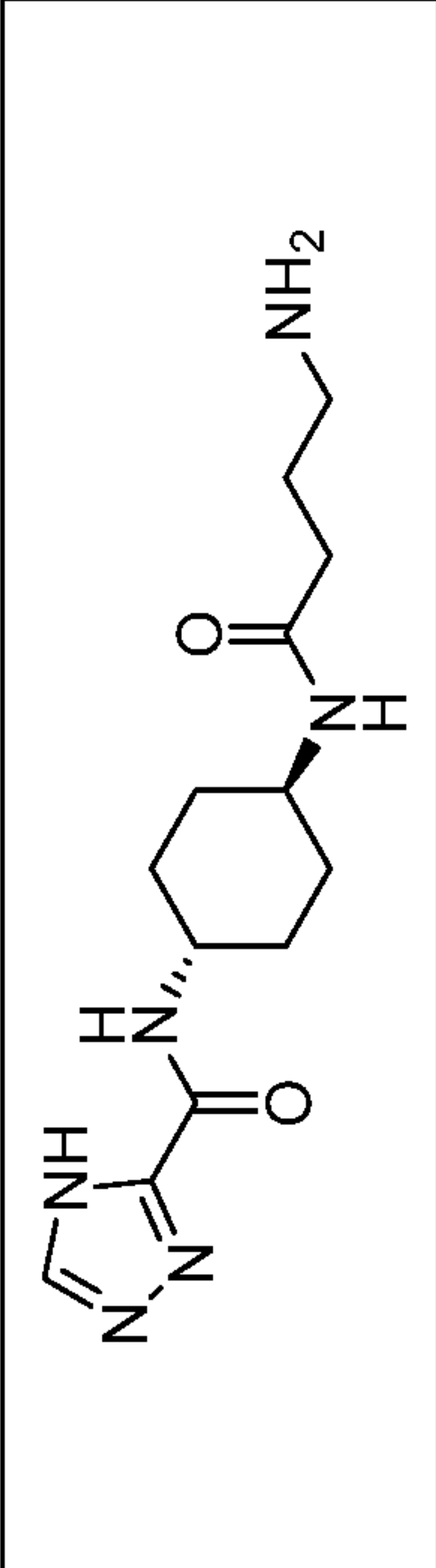
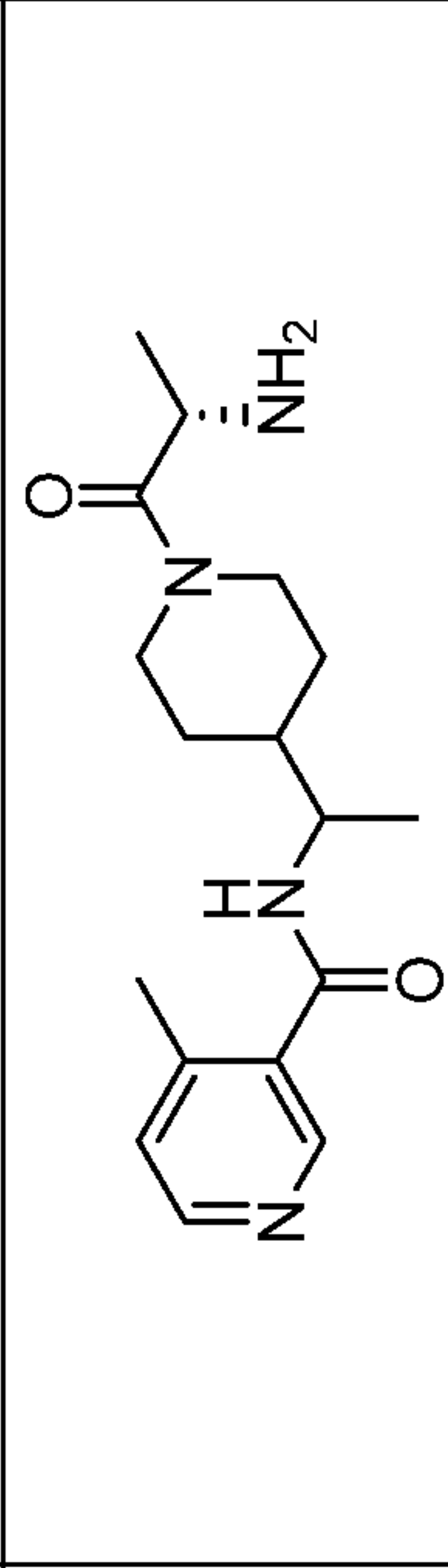
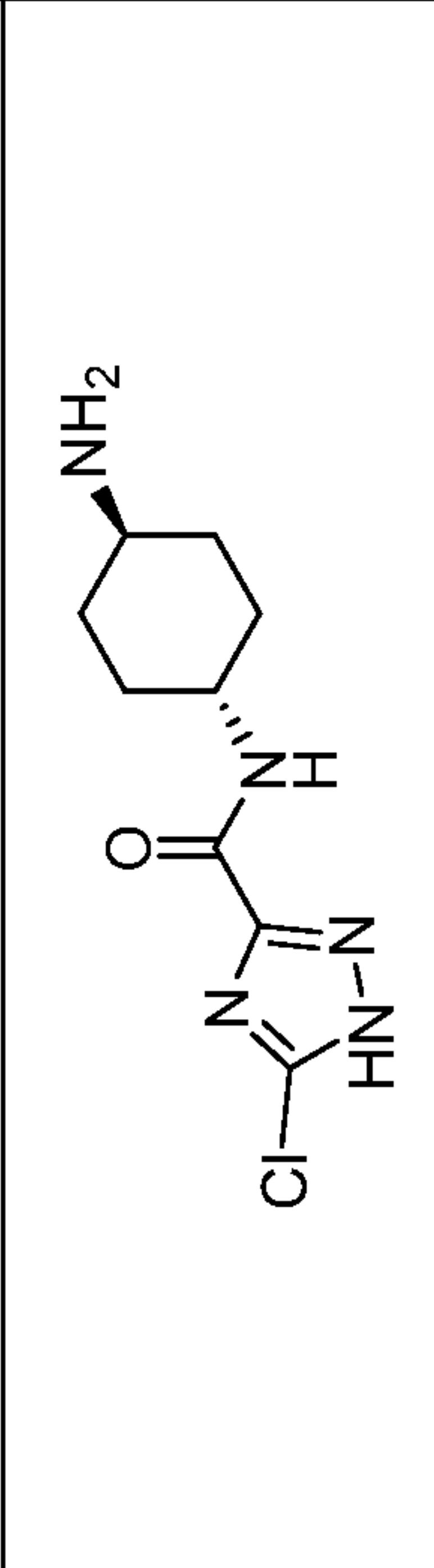
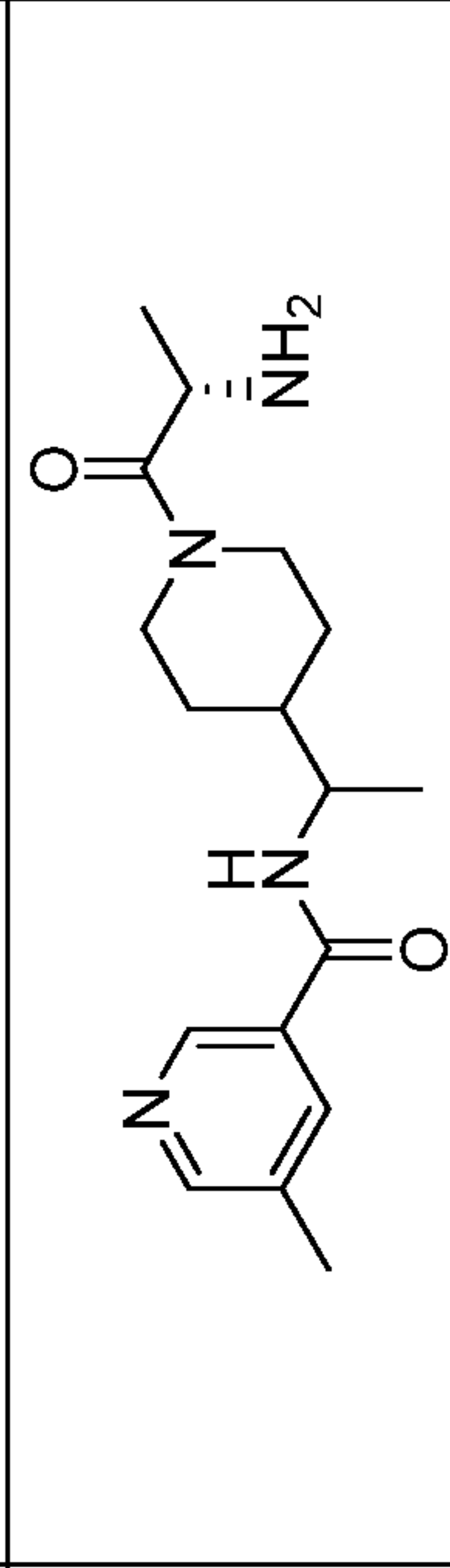
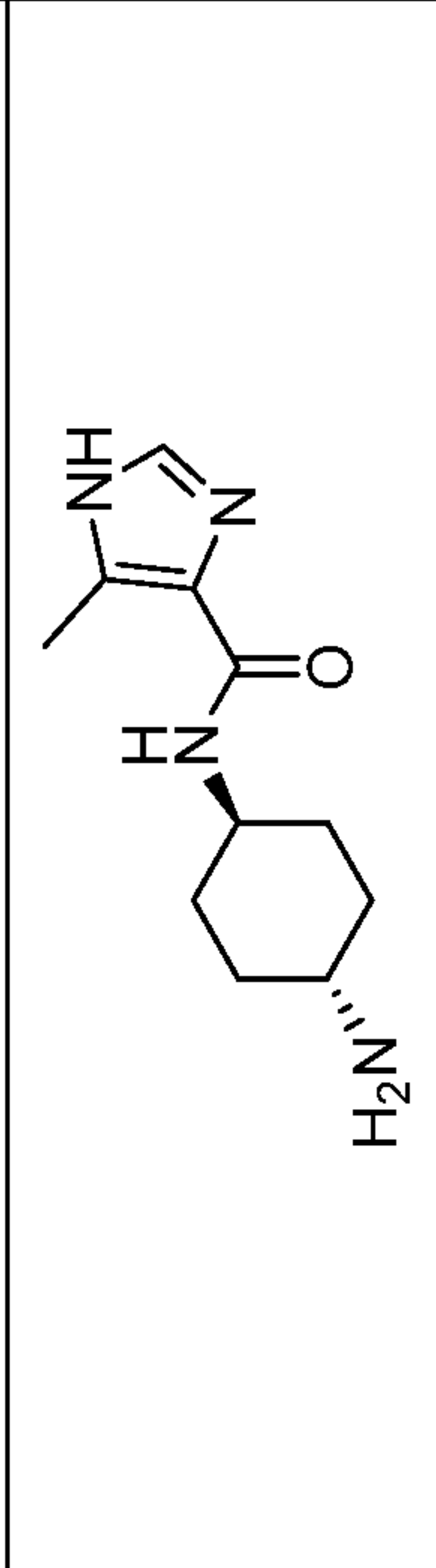
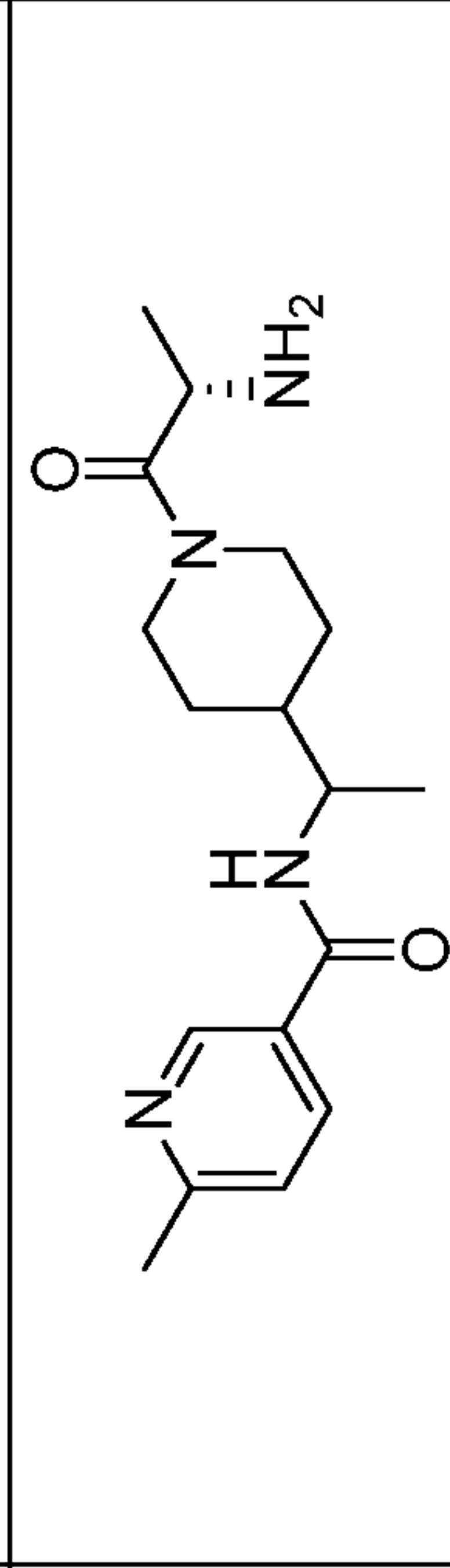
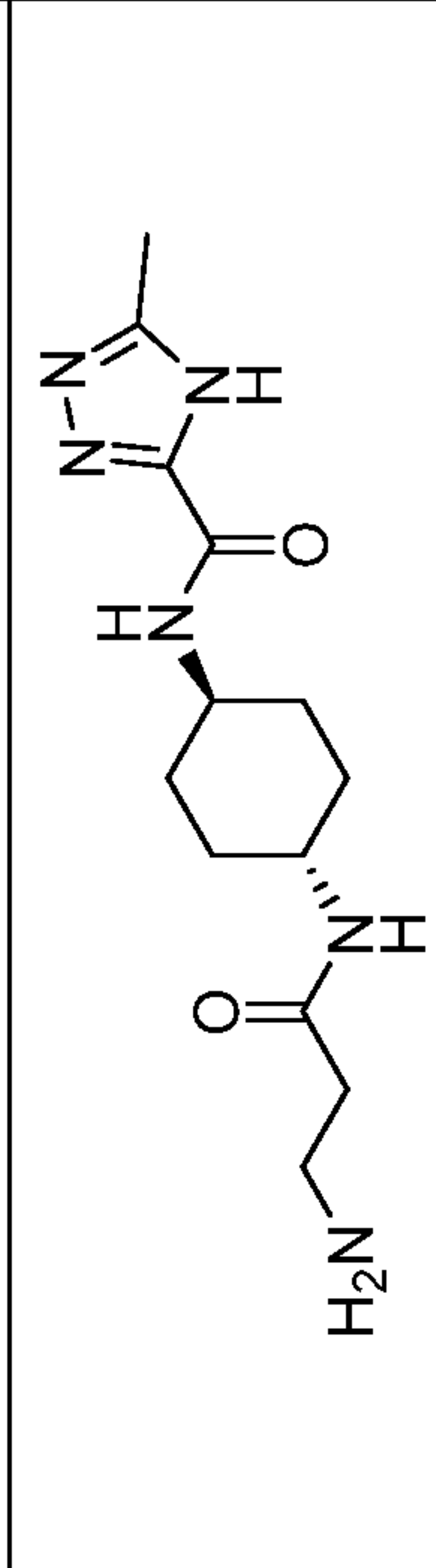
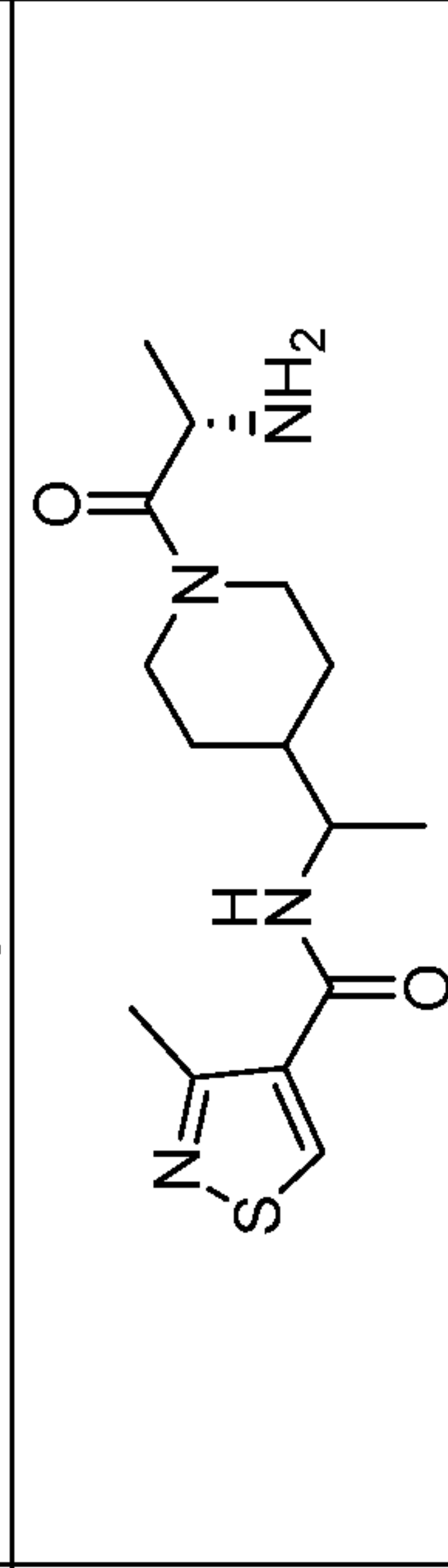
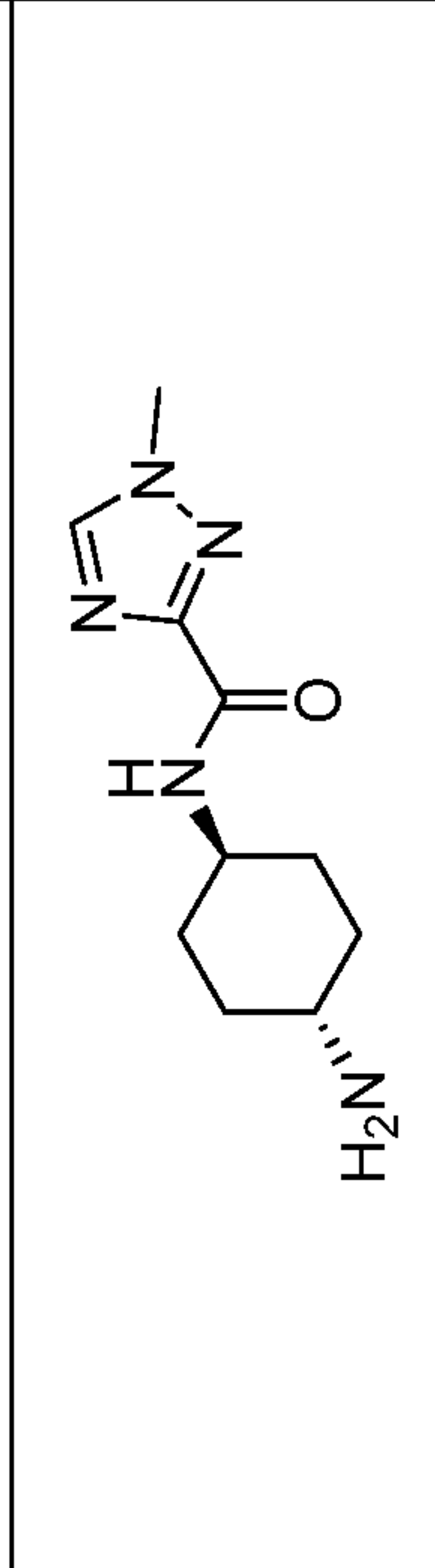
228		TFA	513		None
229		HCl	514		None
230		HCl	515		TFA
231		HCl	516		None
232		HCl	517		None

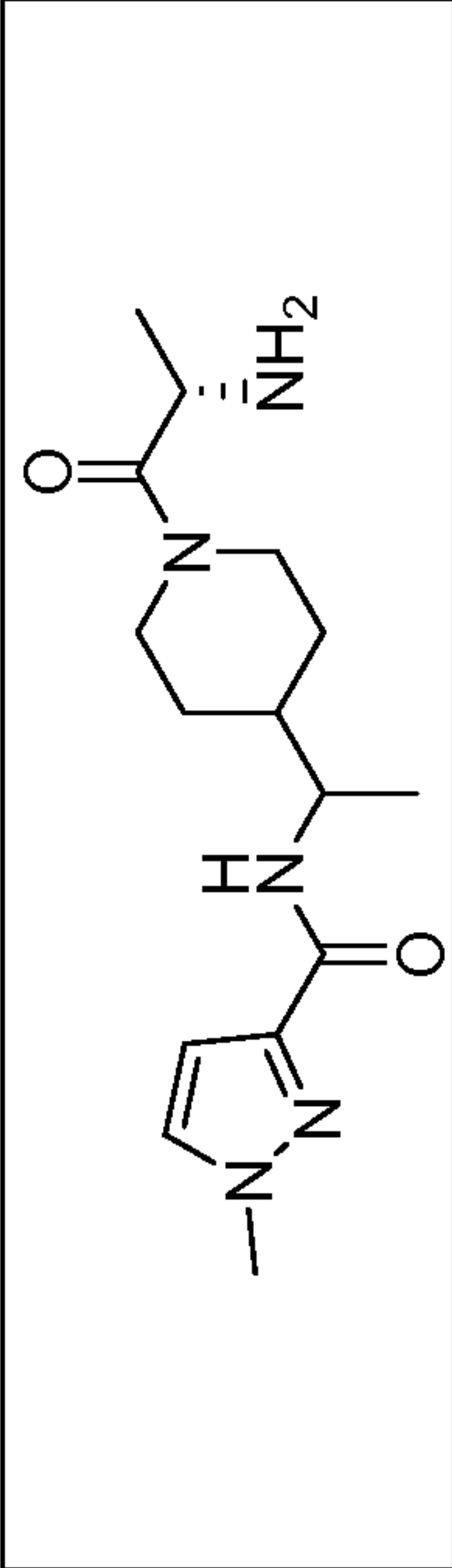
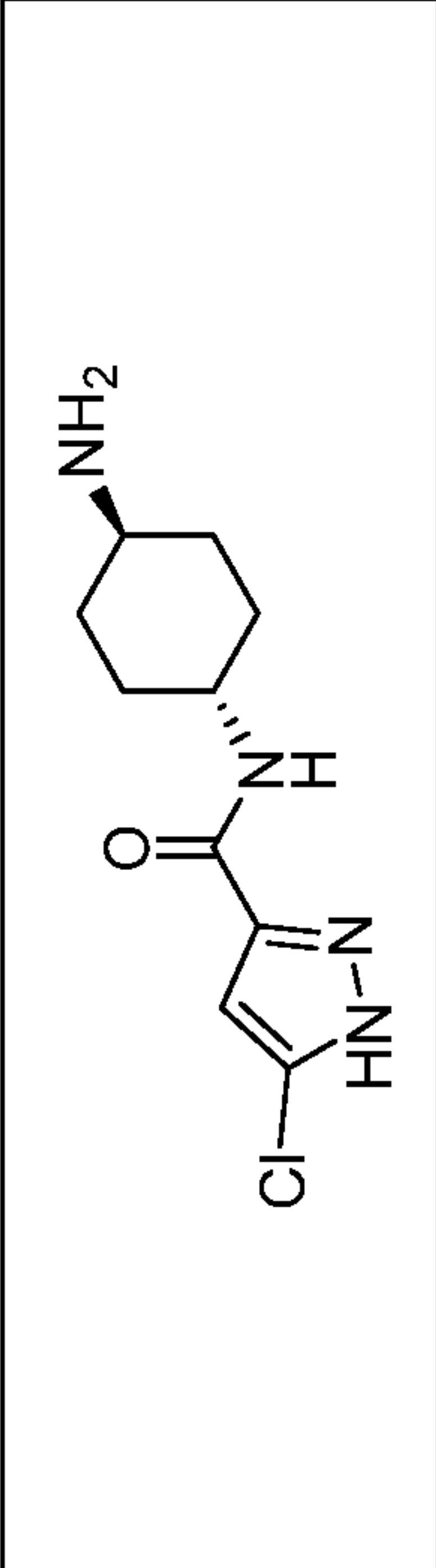
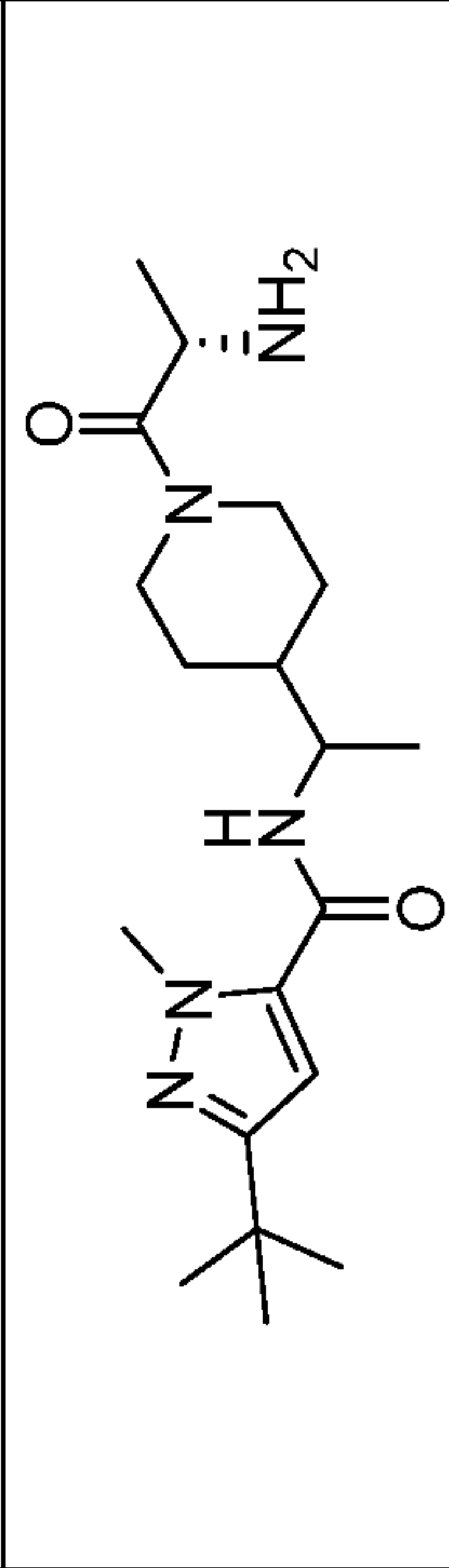
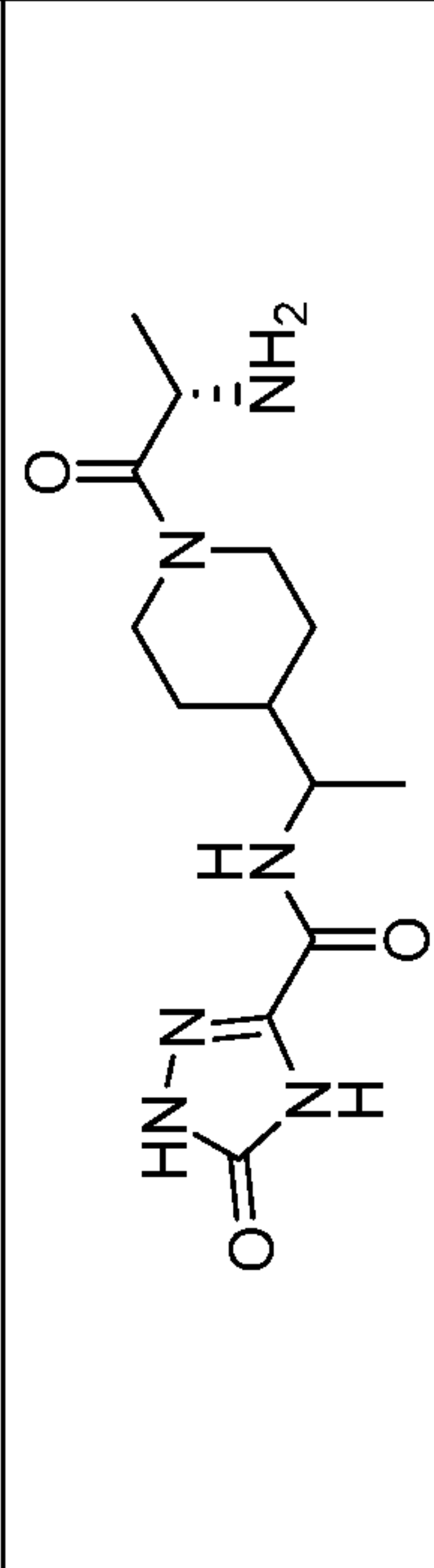
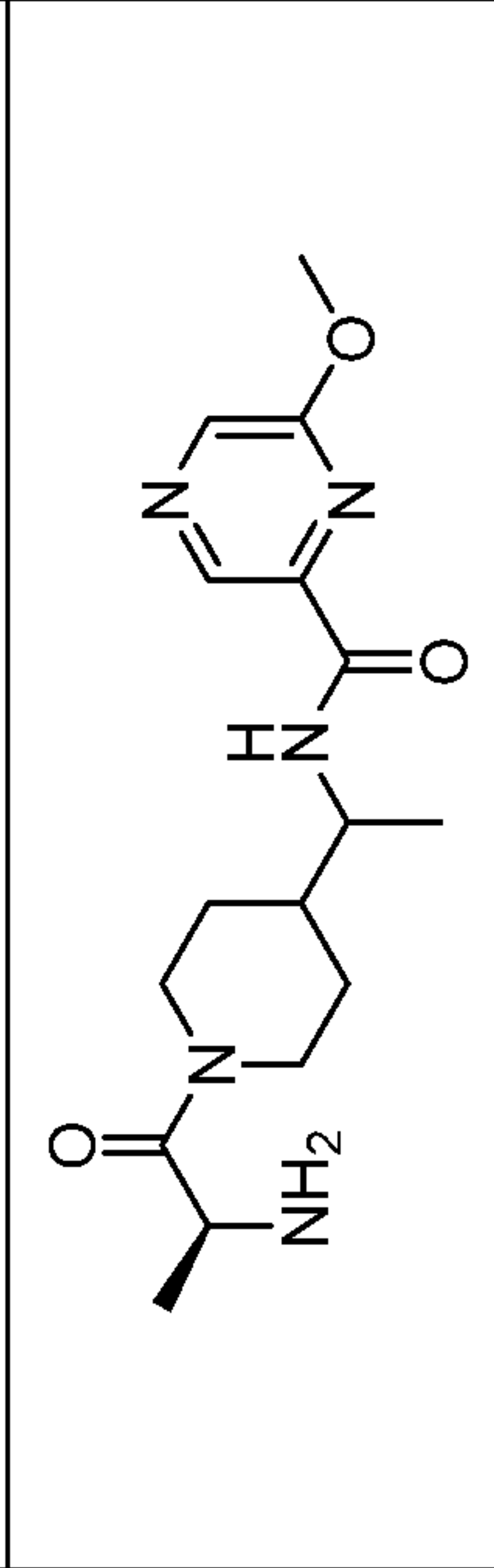
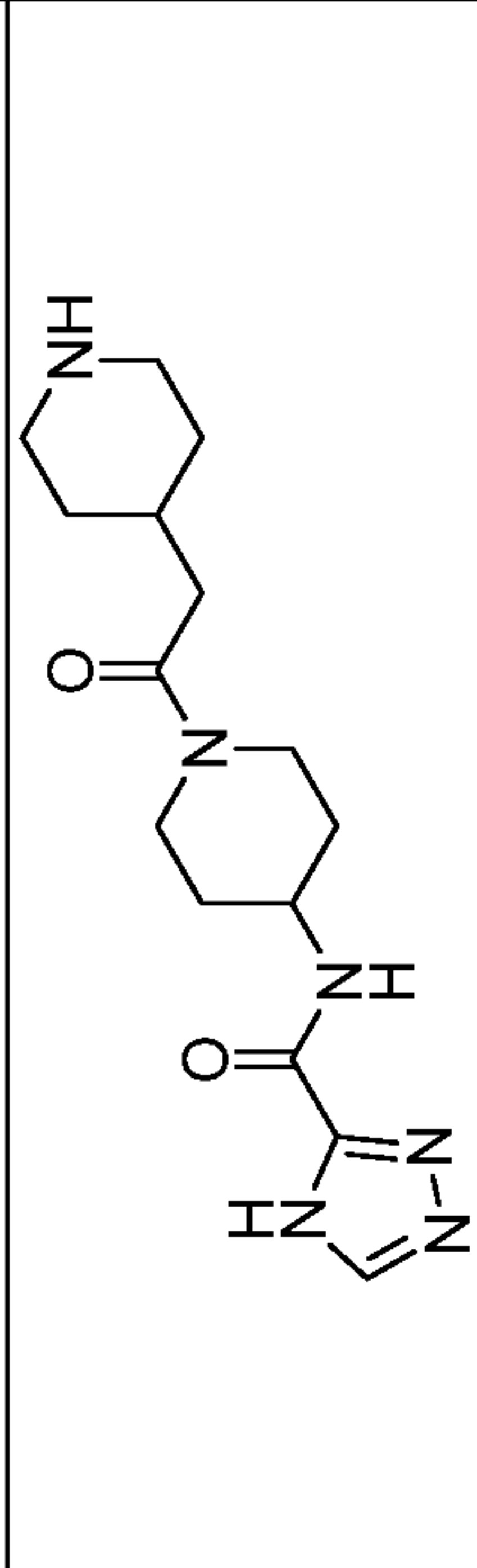
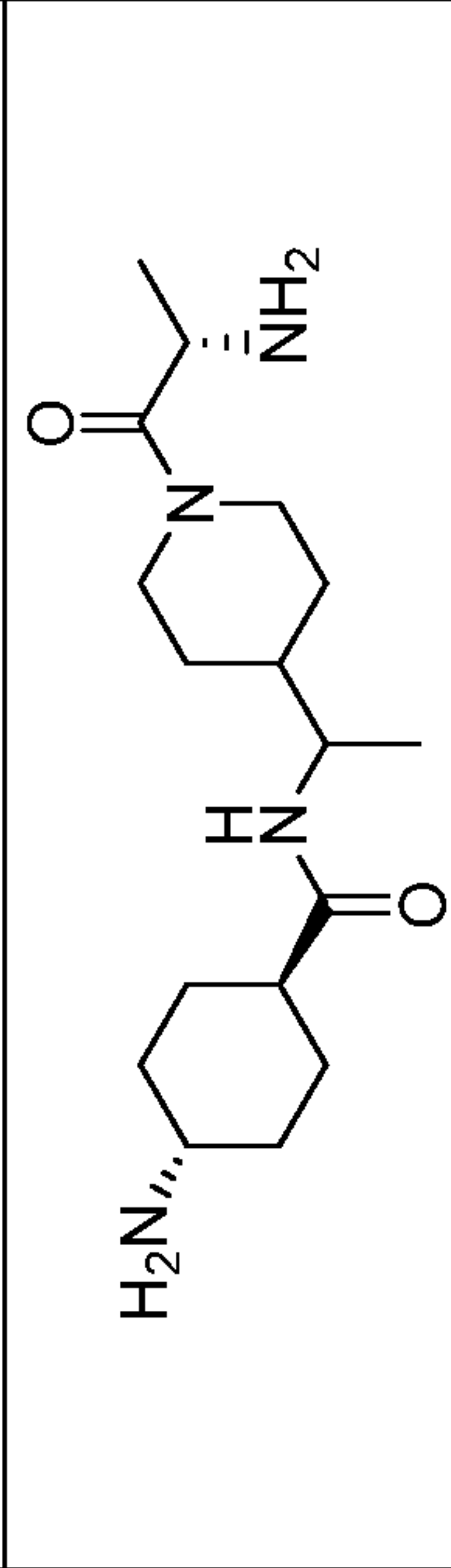
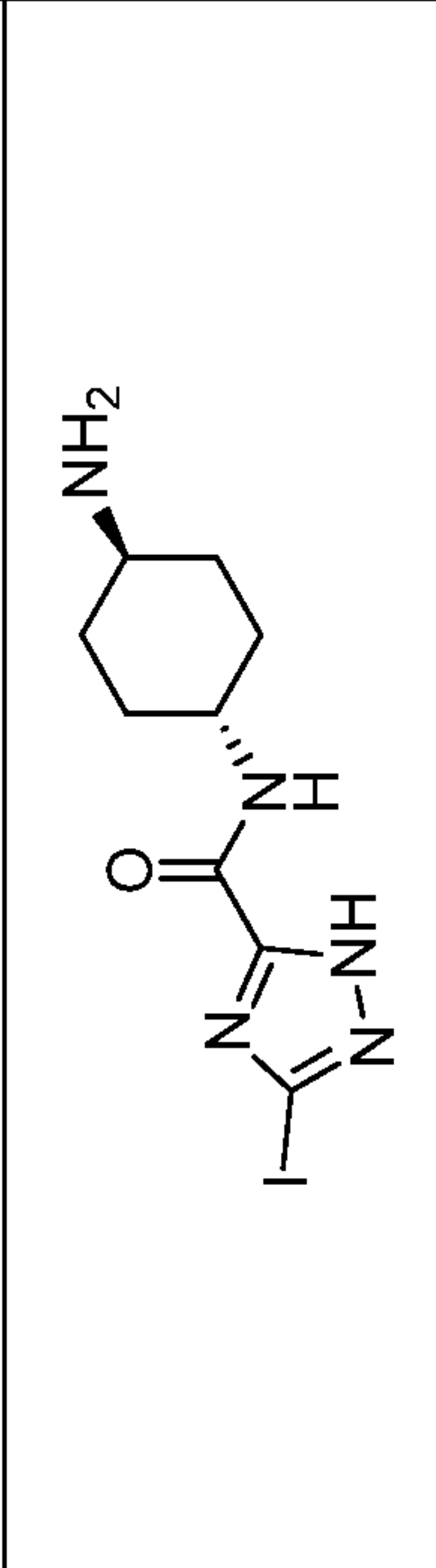
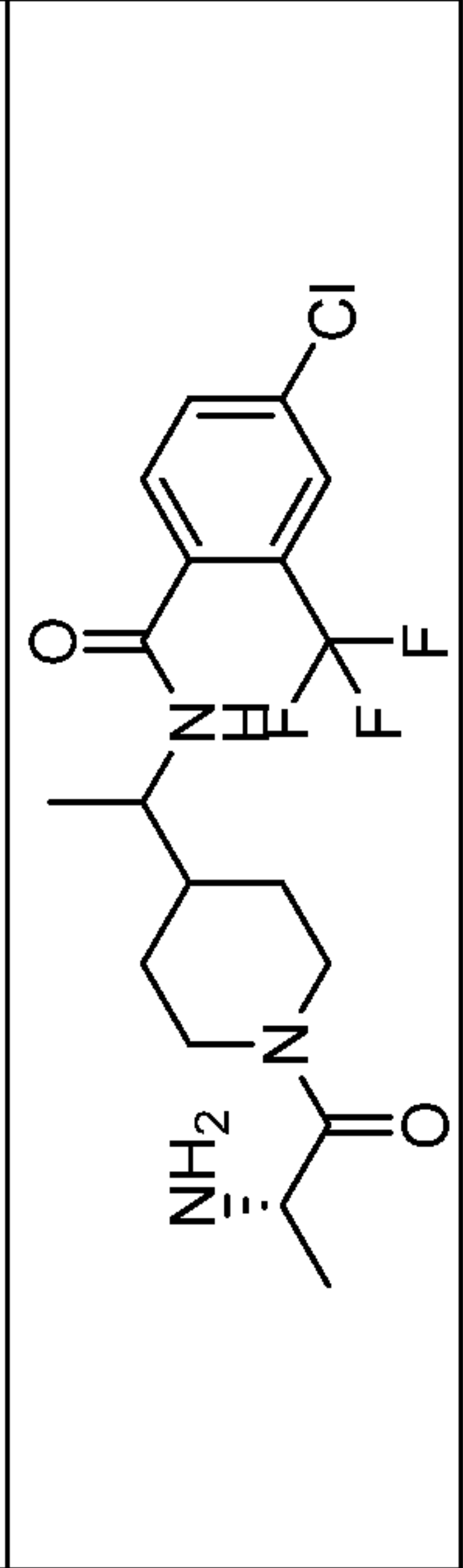
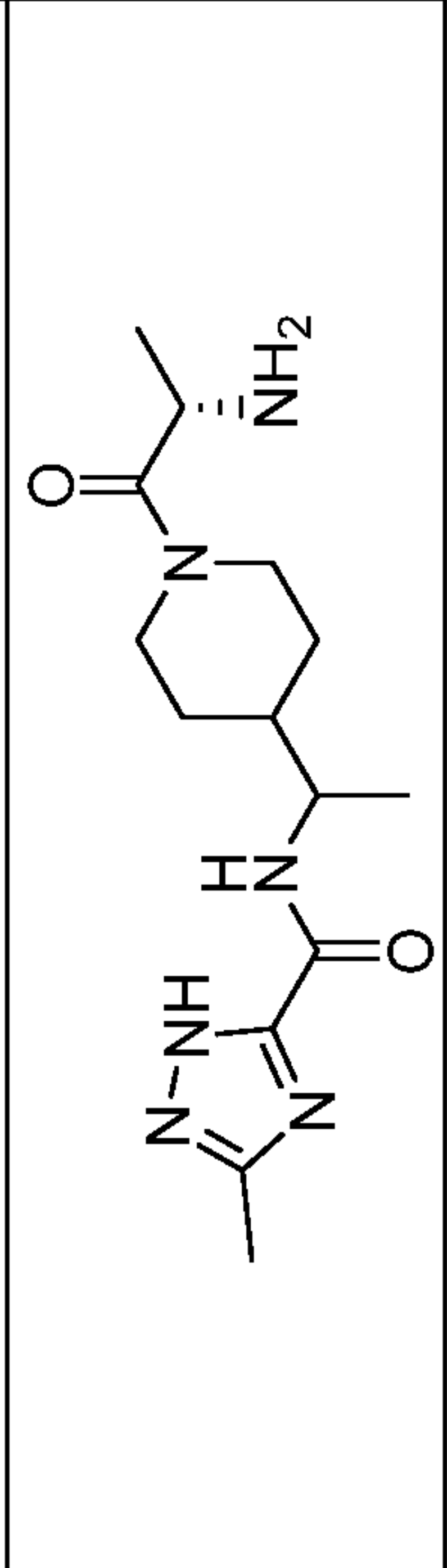
233		HCl	518		None
234		HCl	519		TFA
235		HCl	520		TFA
236		TFA	521		None
237		TFA	522		None

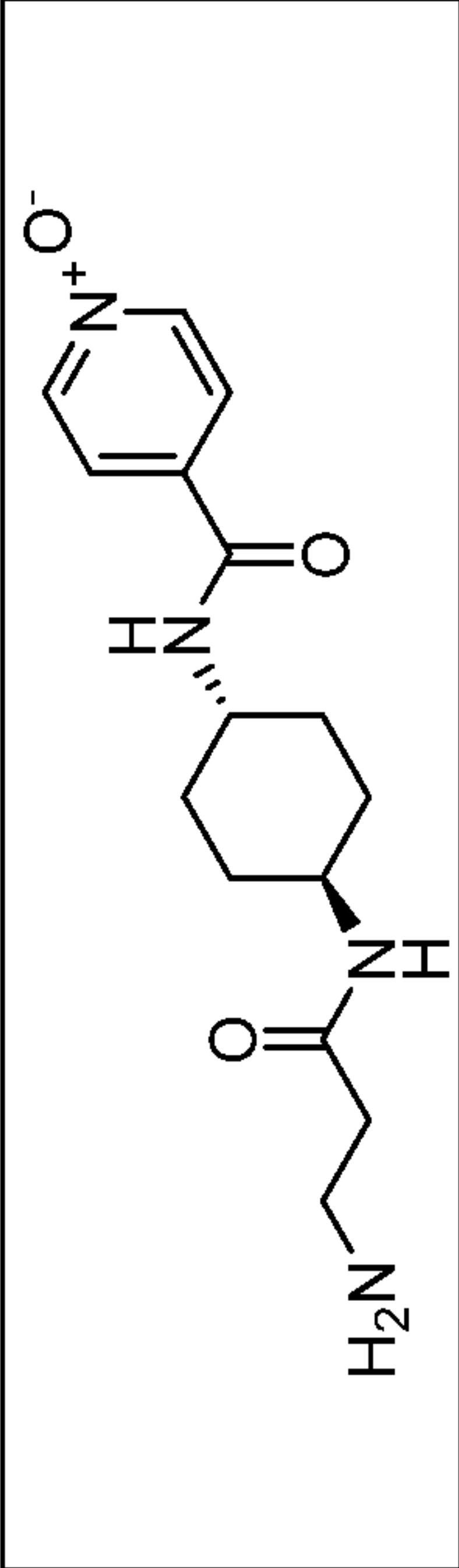
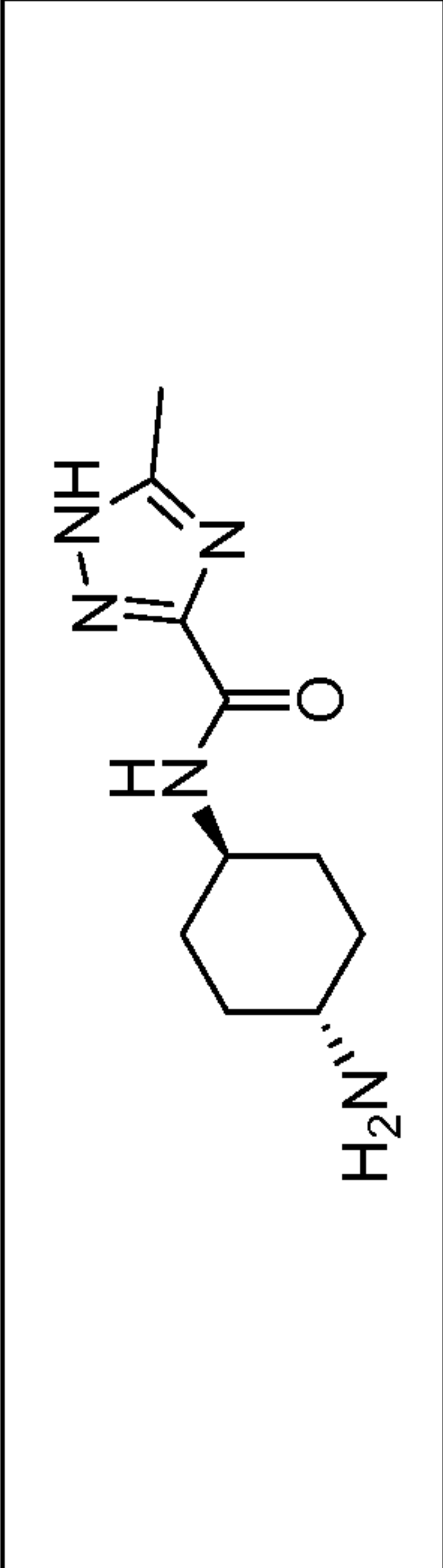
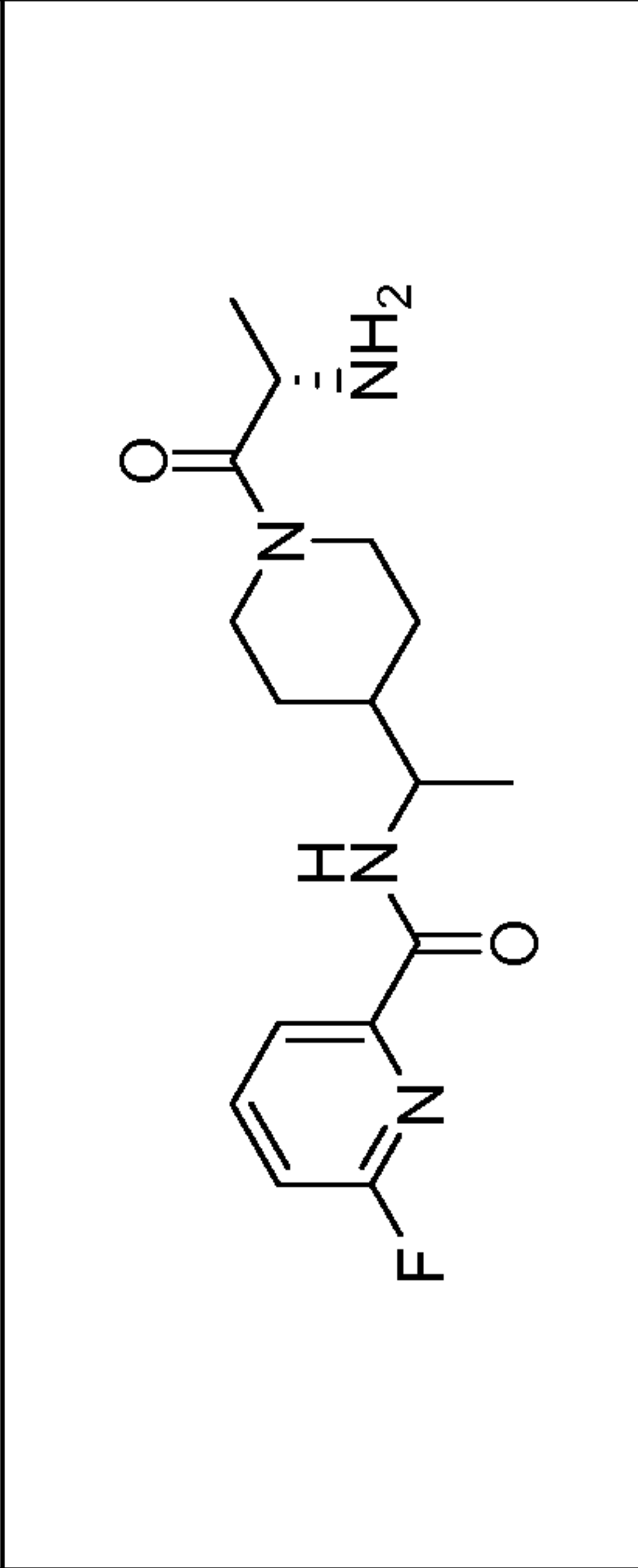
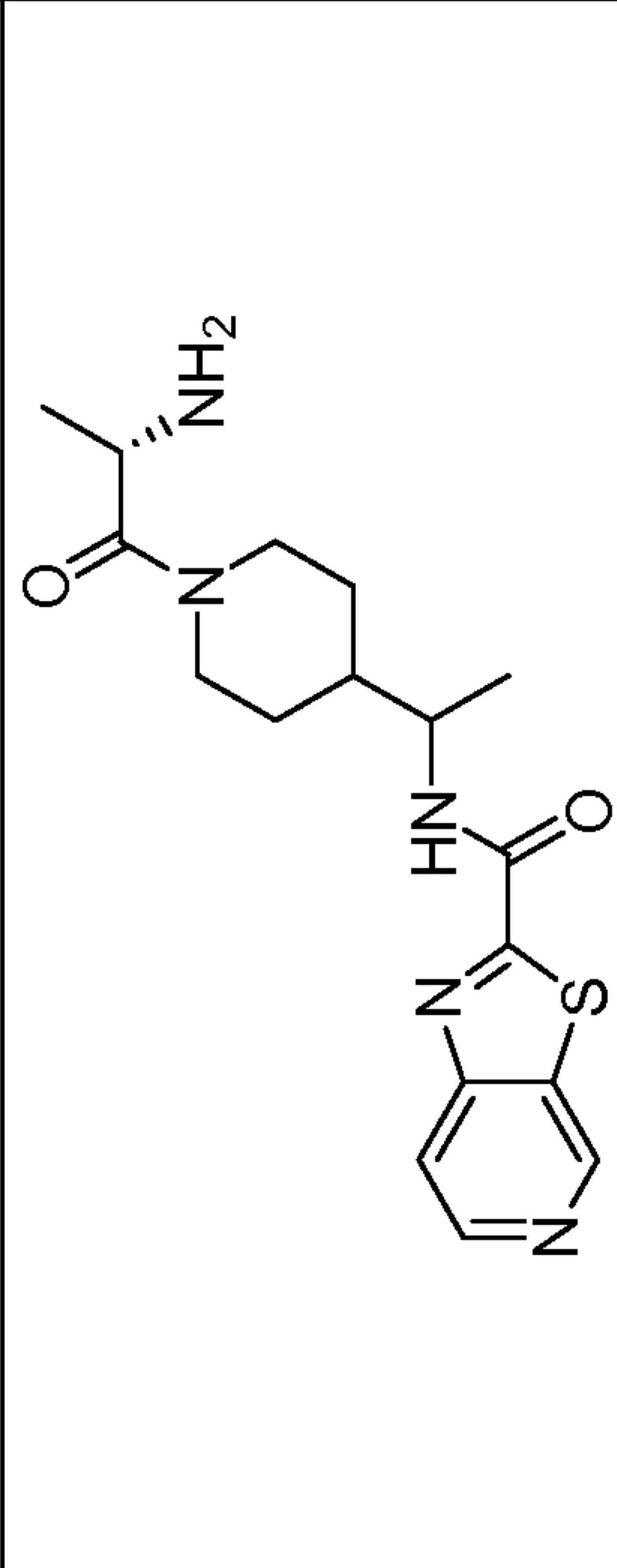
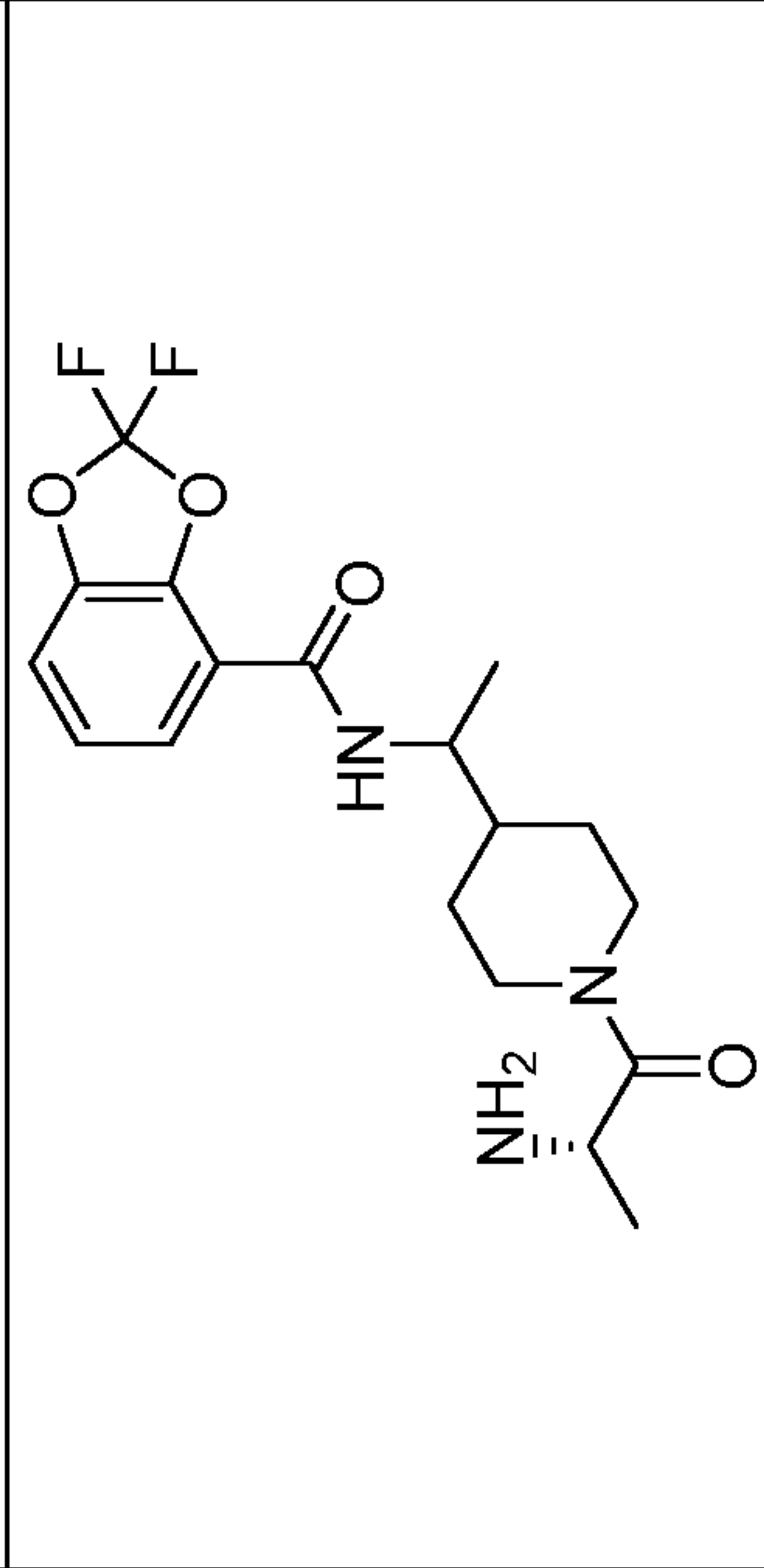
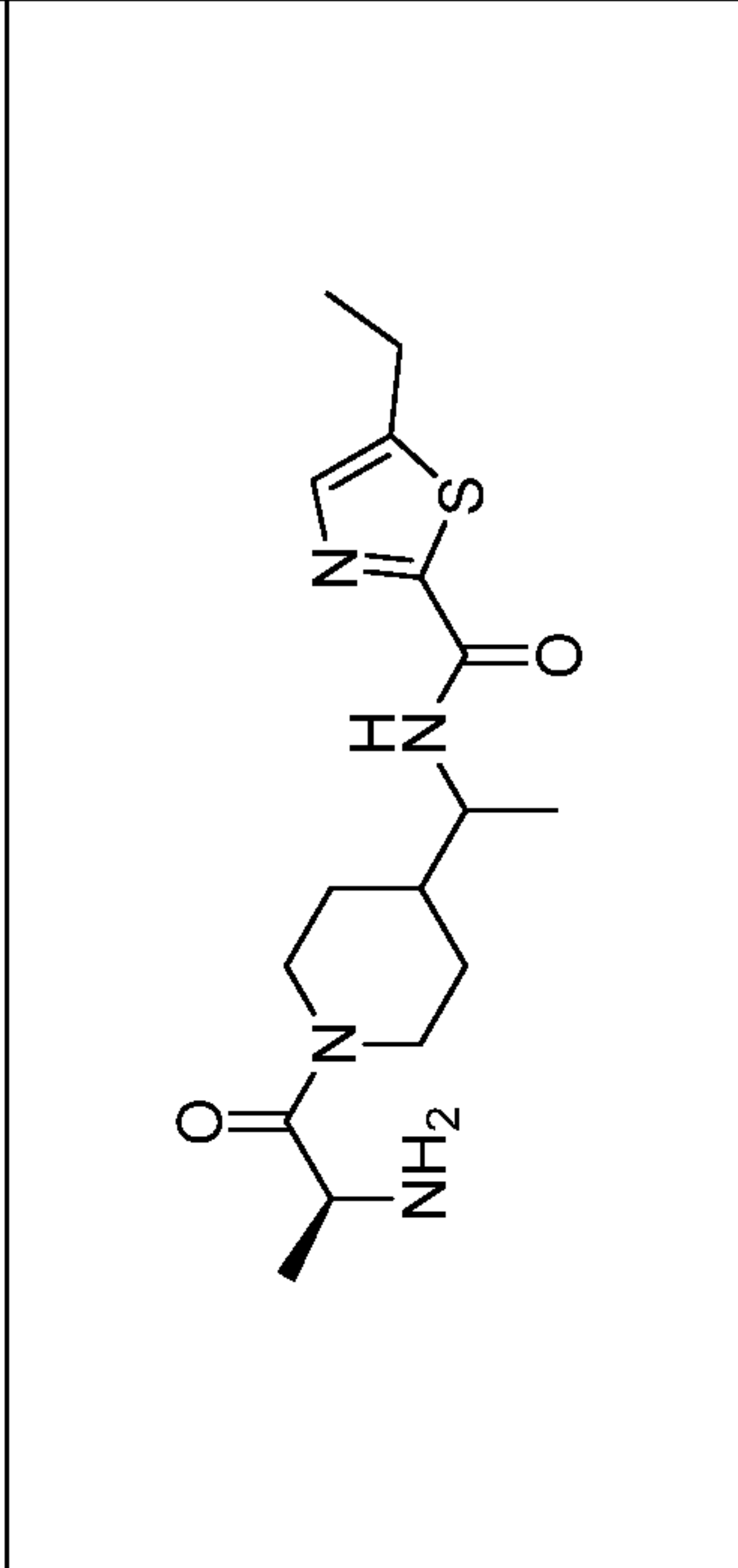
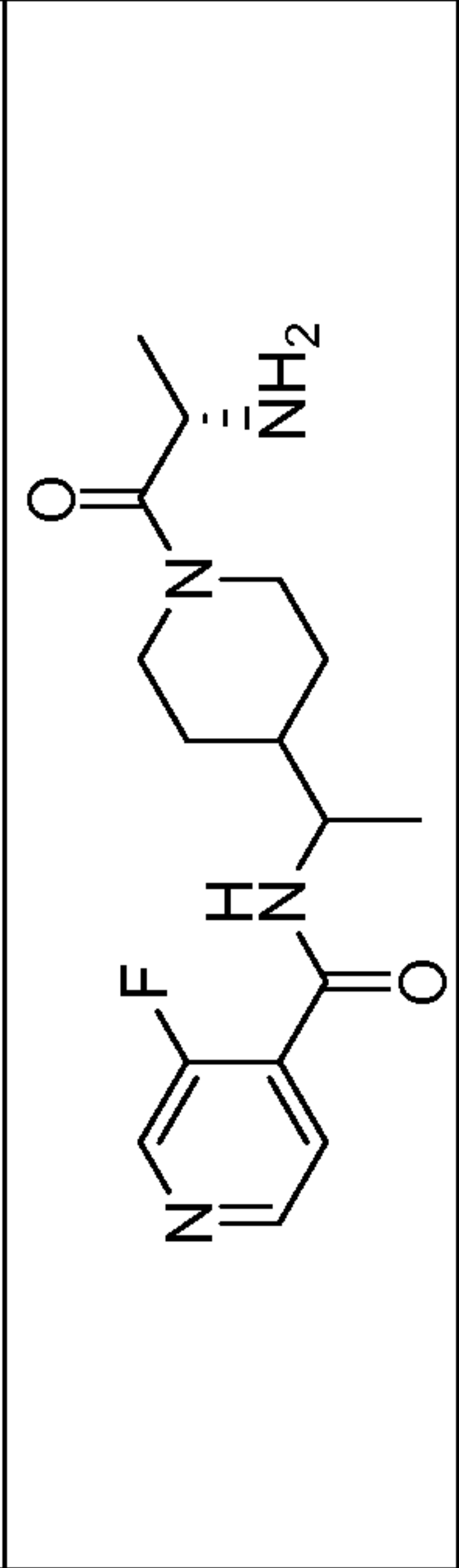
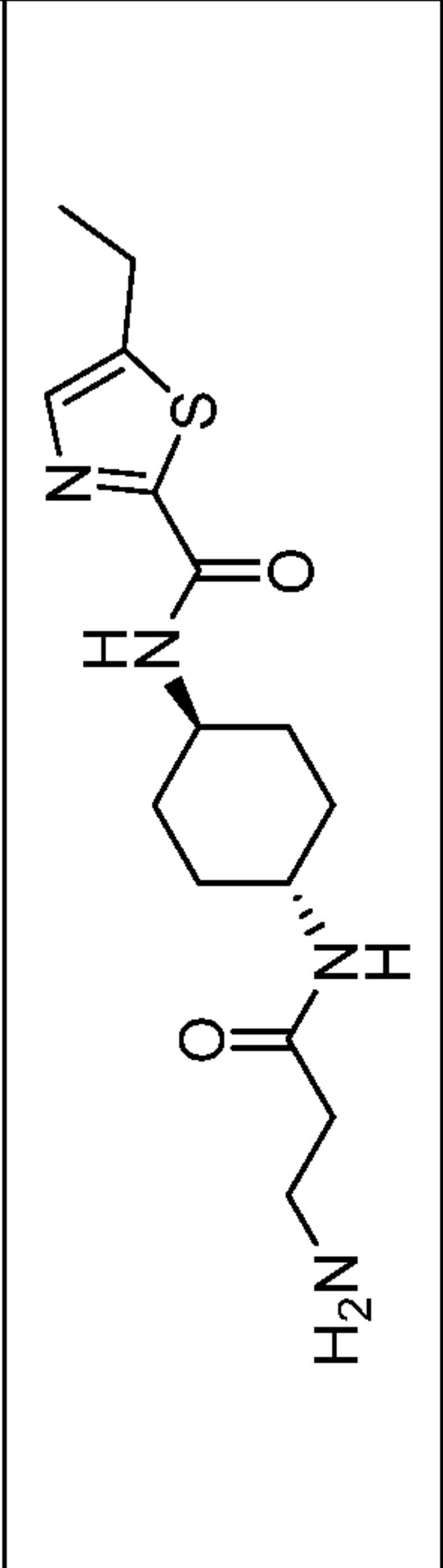
238		TFA	523		HCl
239		TFA	525		HCl
241		TFA	527		TFA
242		None	528		TFA
243		TFA	529		TFA

244		HCl	530		TFA
245		HCl	531		TFA
246		HCl	532		TFA
247		TFA	533		TFA
248		None	534		None

249		TFA	535		None
250		TFA	536		None
251		HCl	537		None
252		HCl	538		TFA
253		TFA	539		None

254		TFA	540		TFA
255		TFA	541		TFA
256		TFA	542		None
257		TFA	543		TFA
258		TFA	544		TFA

259		TFA	545		TFA
260		TFA	546		TFA
261		TFA	547		None
262		HCl	548		TFA
263		TFA	549		TFA

264		HCl	550		TFA
265		TFA	551		TFA
266		TFA	552		TFA
267		TFA	553		TFA

268		TFA	554		TFA
269		HCl	555		TFA
270		HCl	556		TFA
271		HCl	557		HCl
272		HCl	558		HCl

273		TFA	559		HCl
274		TFA	560		TFA
275		TFA	561		TFA
276		TFA	562		TFA
277		TFA	563		HCl

278		TFA	564		HCl
279		TFA	565		TFA
280		TFA	566		TFA
281		HCl	567		HCl
283		HCl	568		HCl

284		TFA	569		HCl
285		HCl	570		HCl
286		TFA	571		HCl
287		TFA	572		TFA
288		None	573		HCl

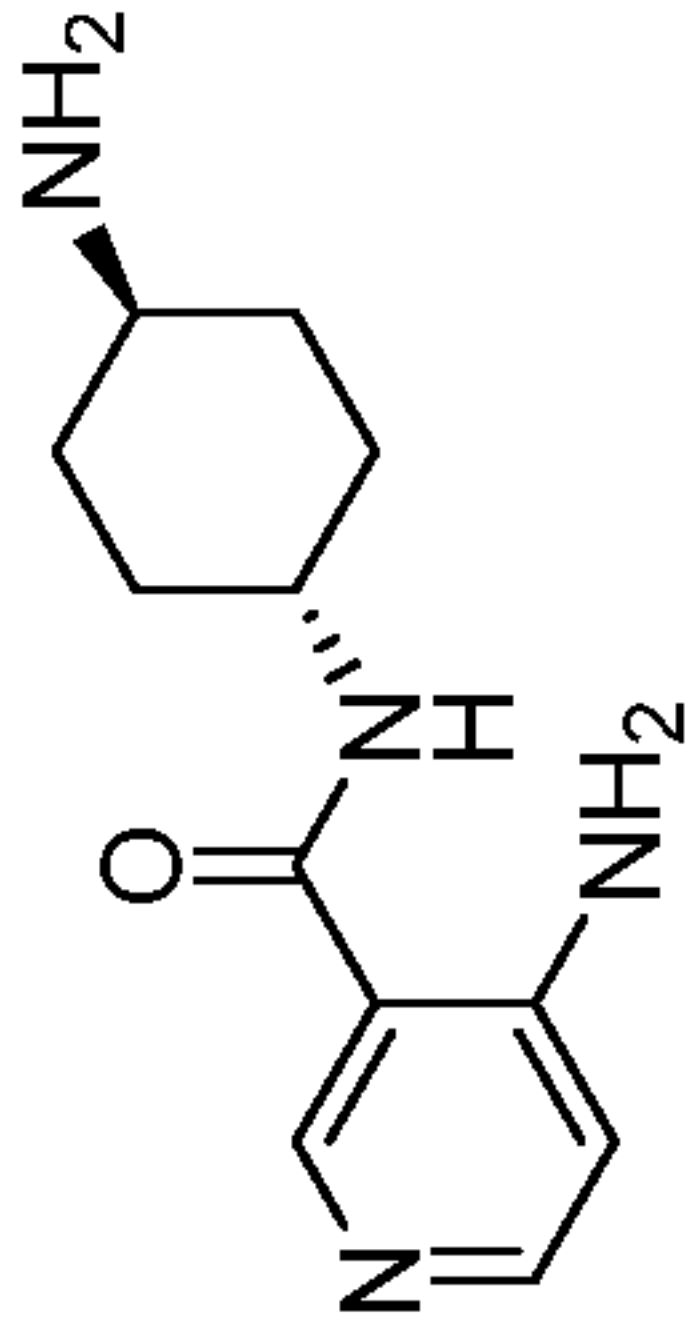
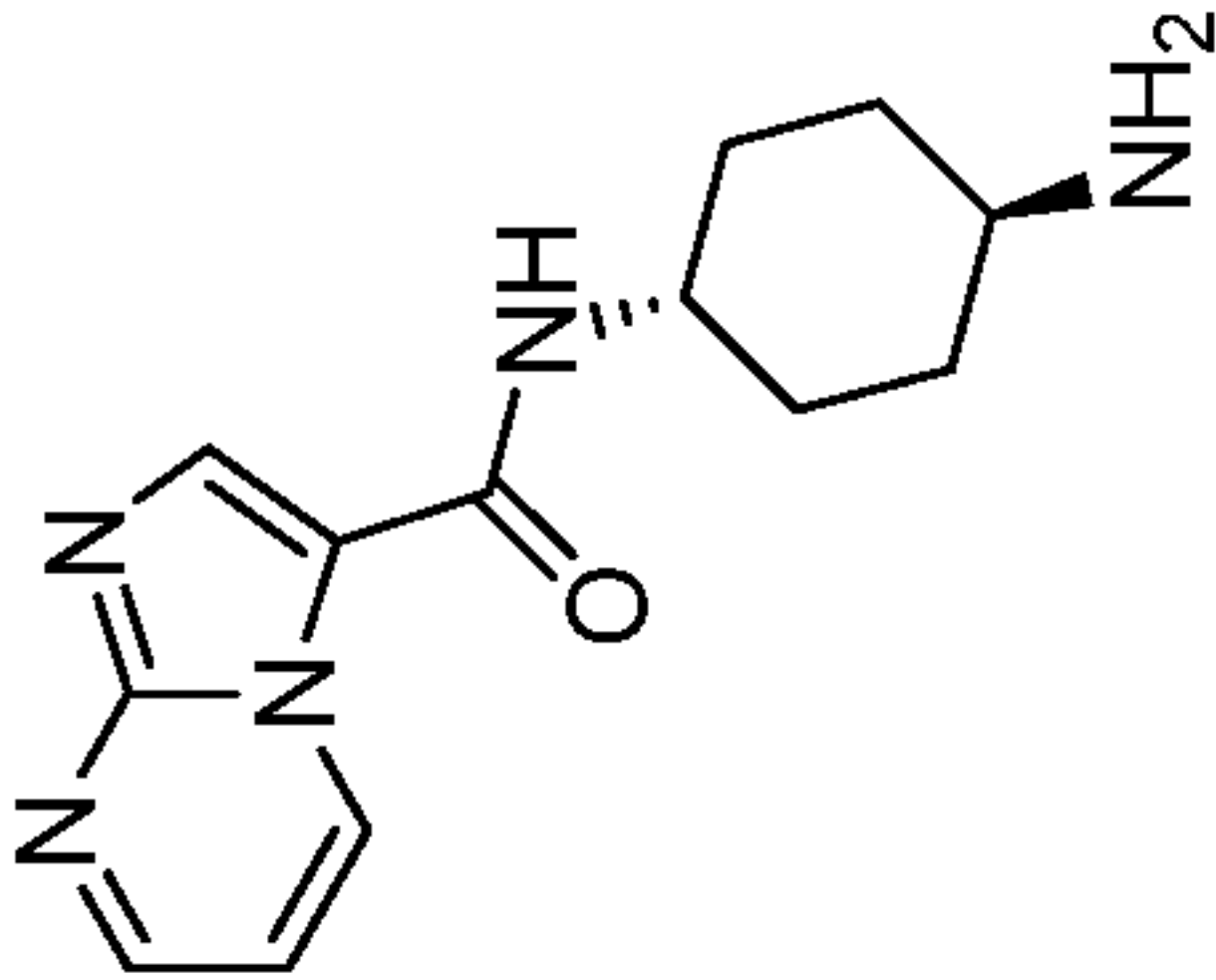
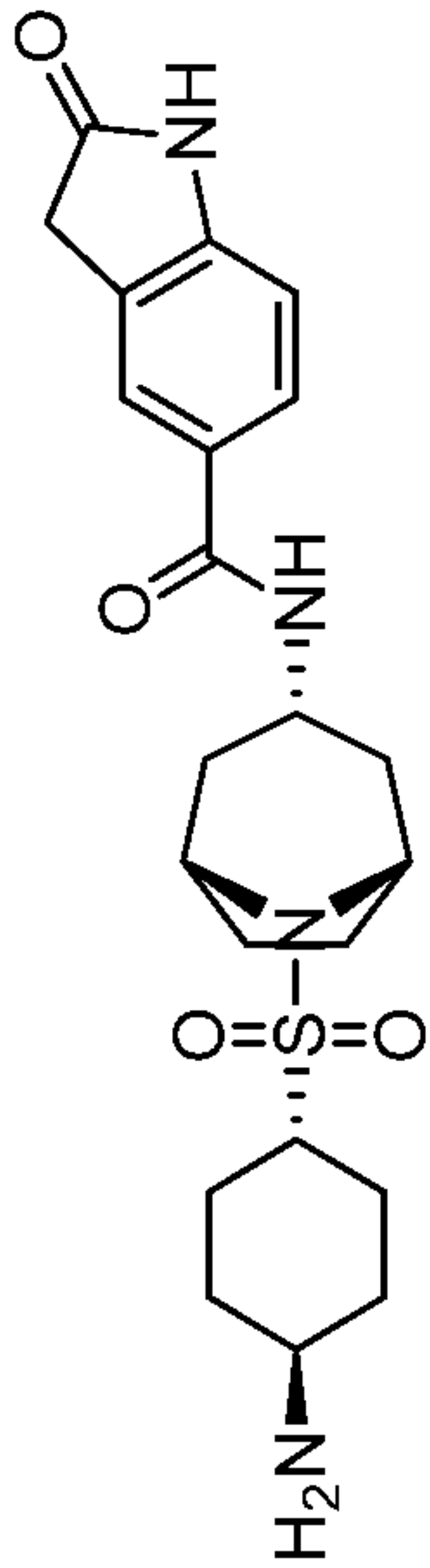
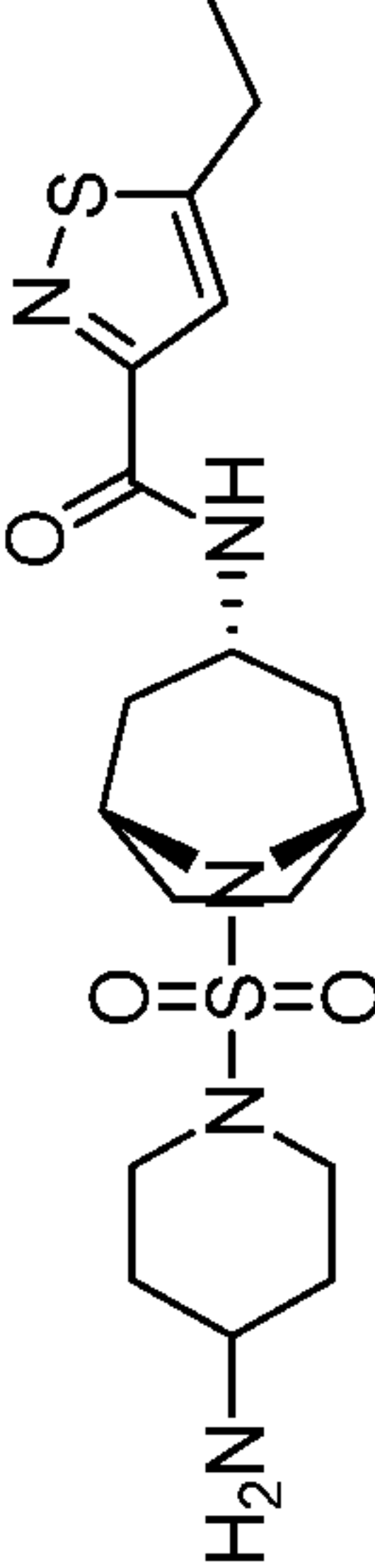
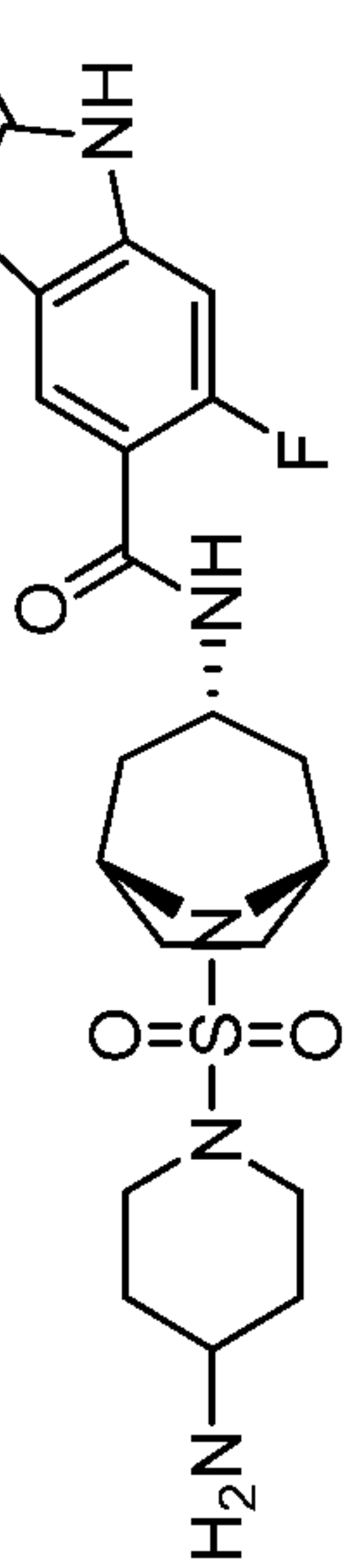
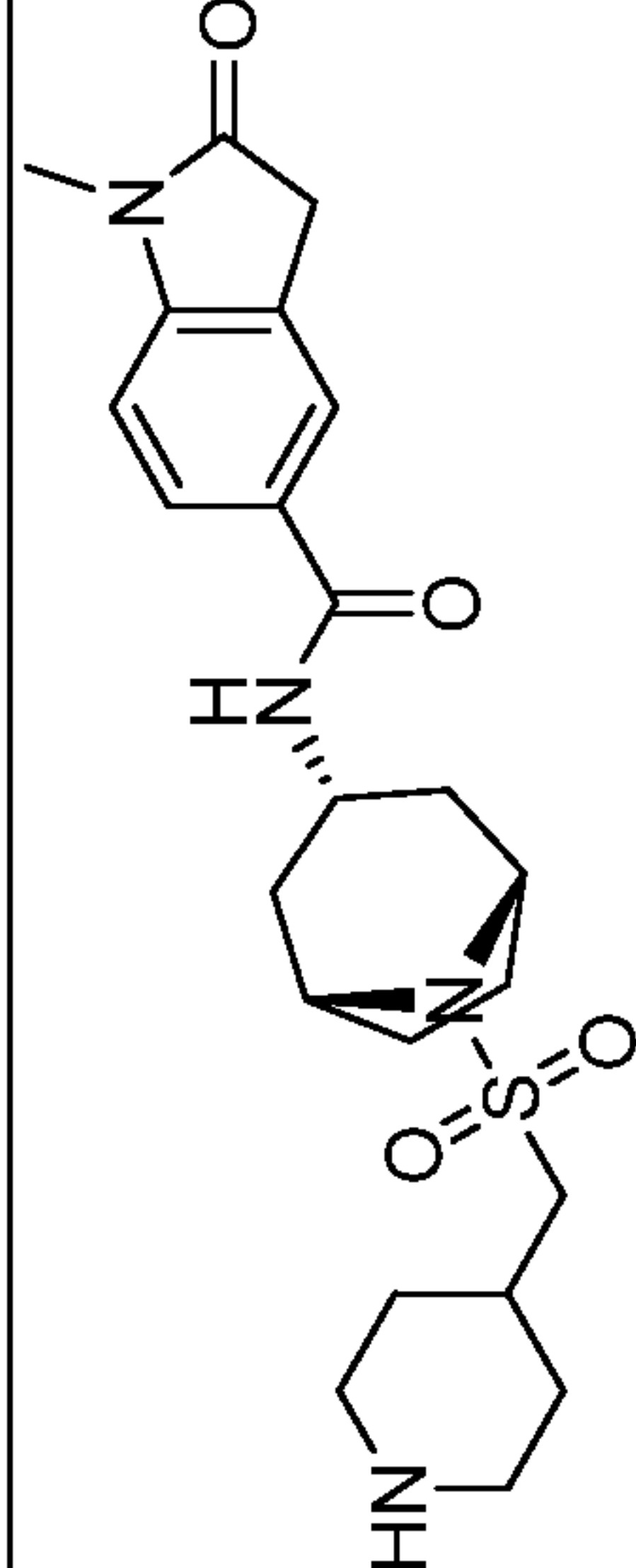
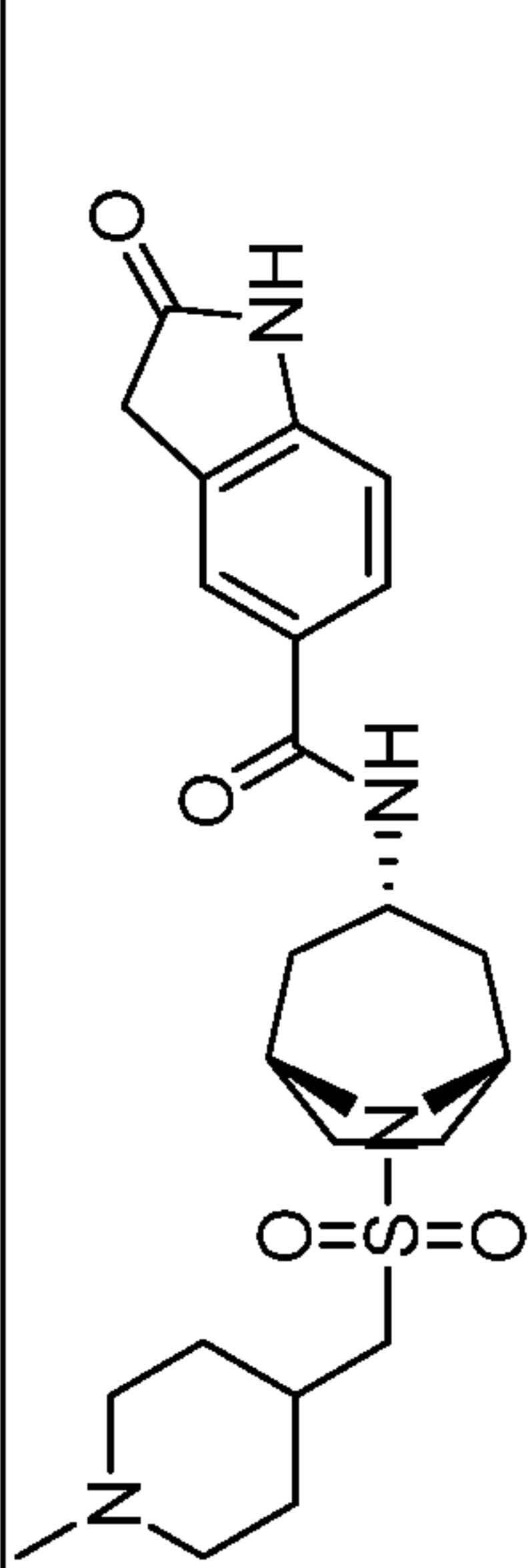
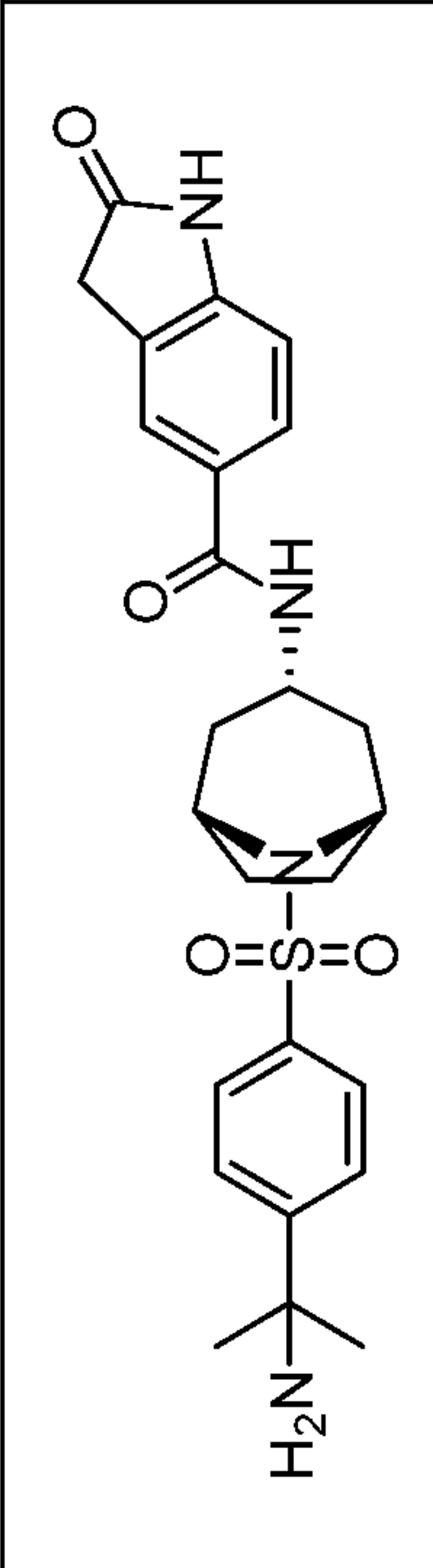
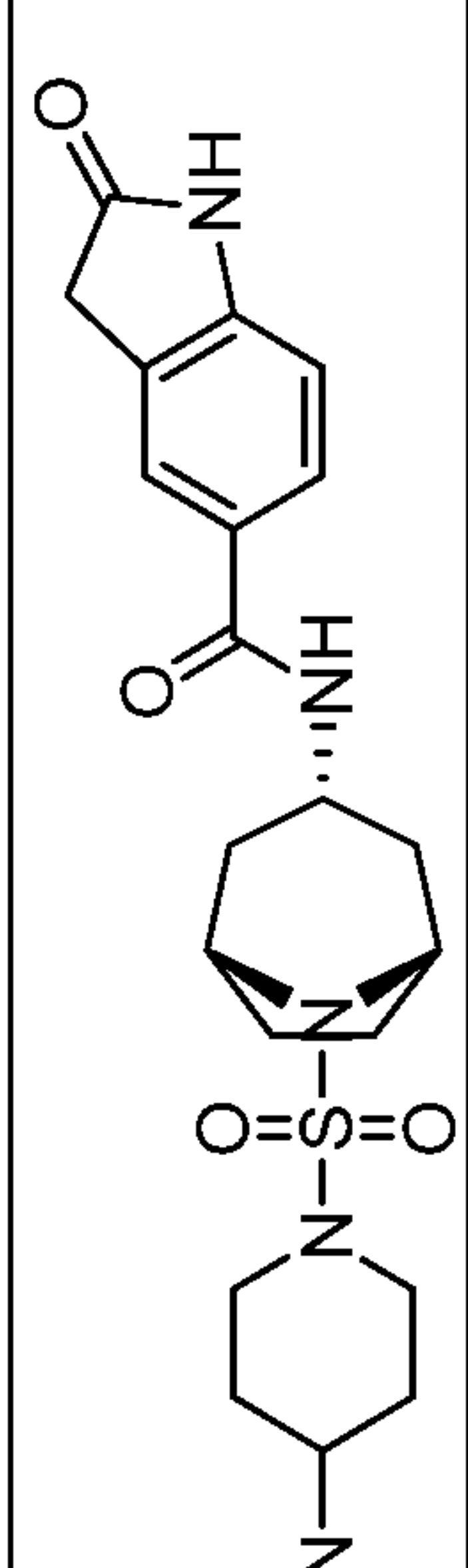
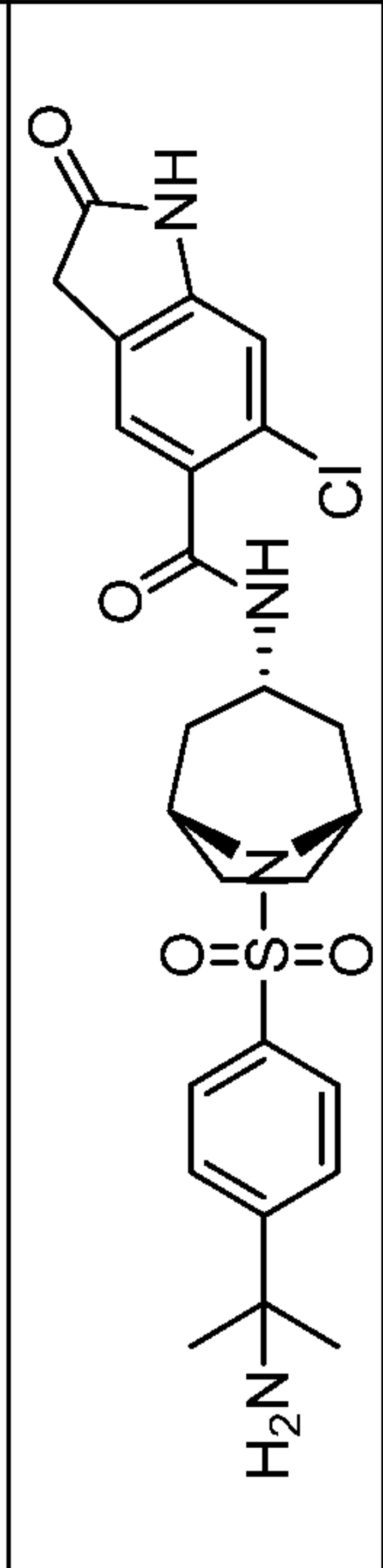
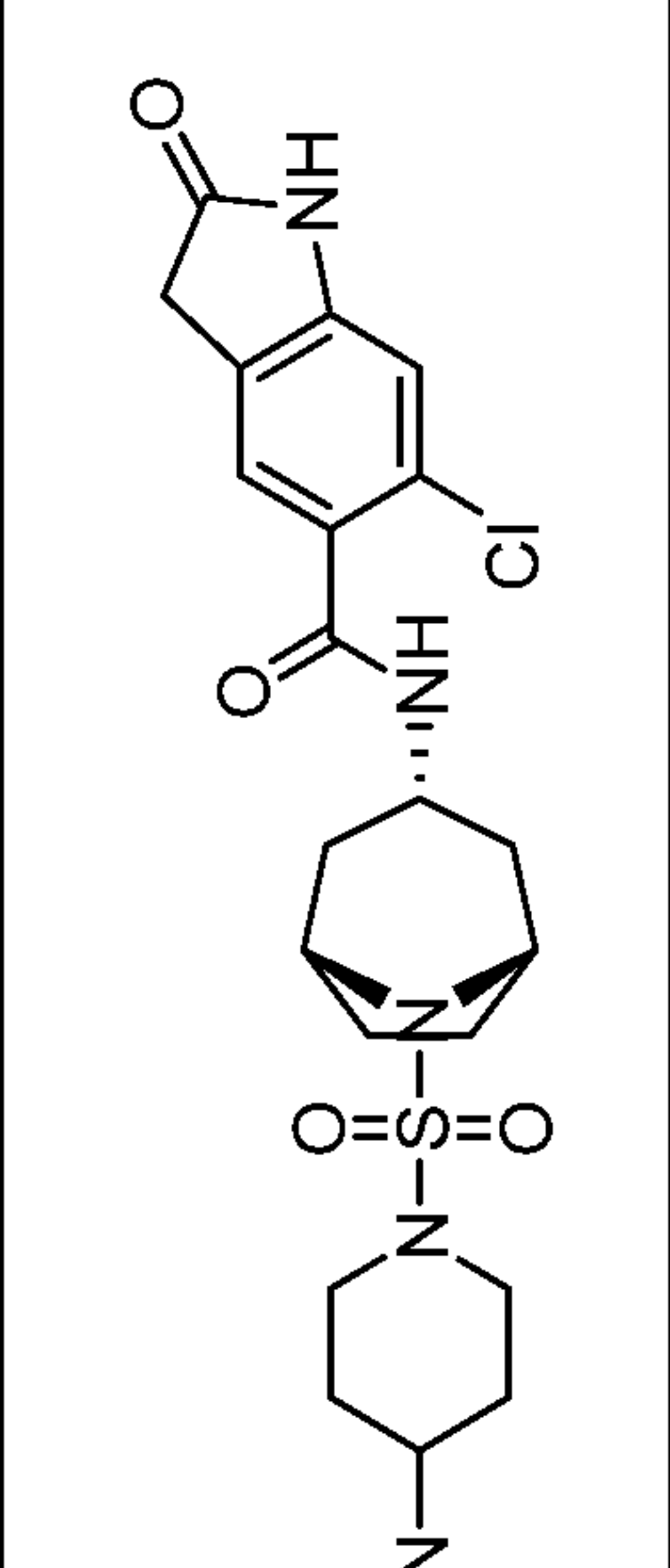
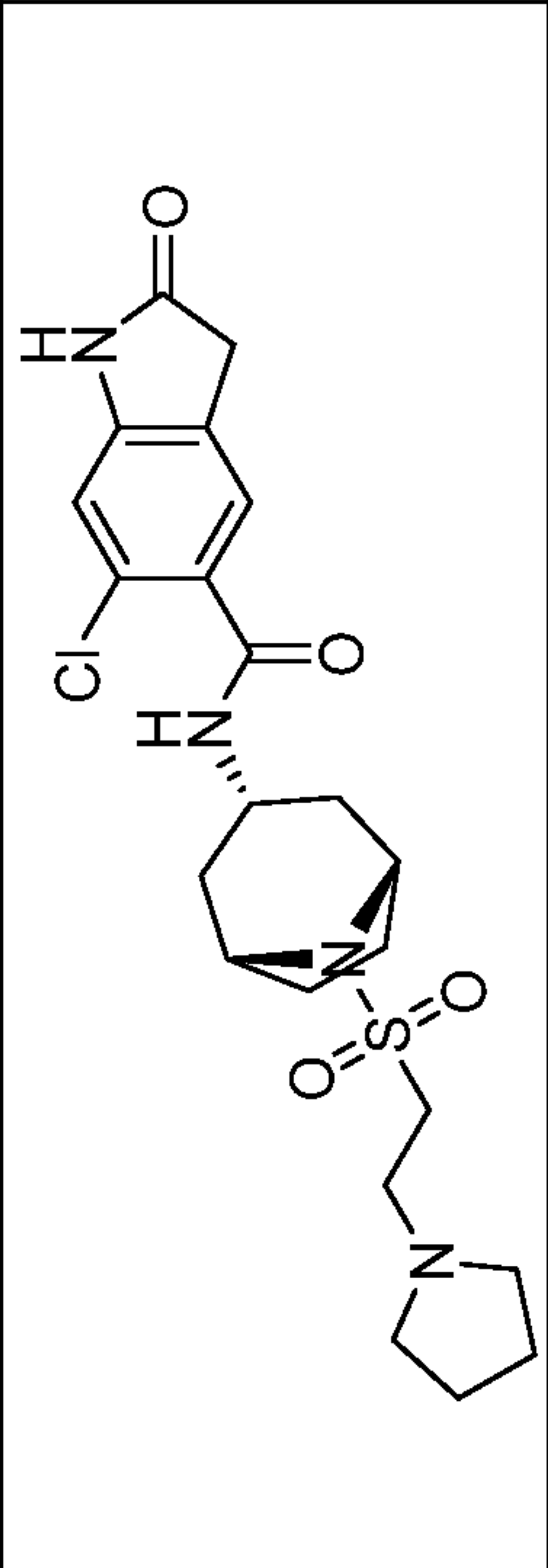
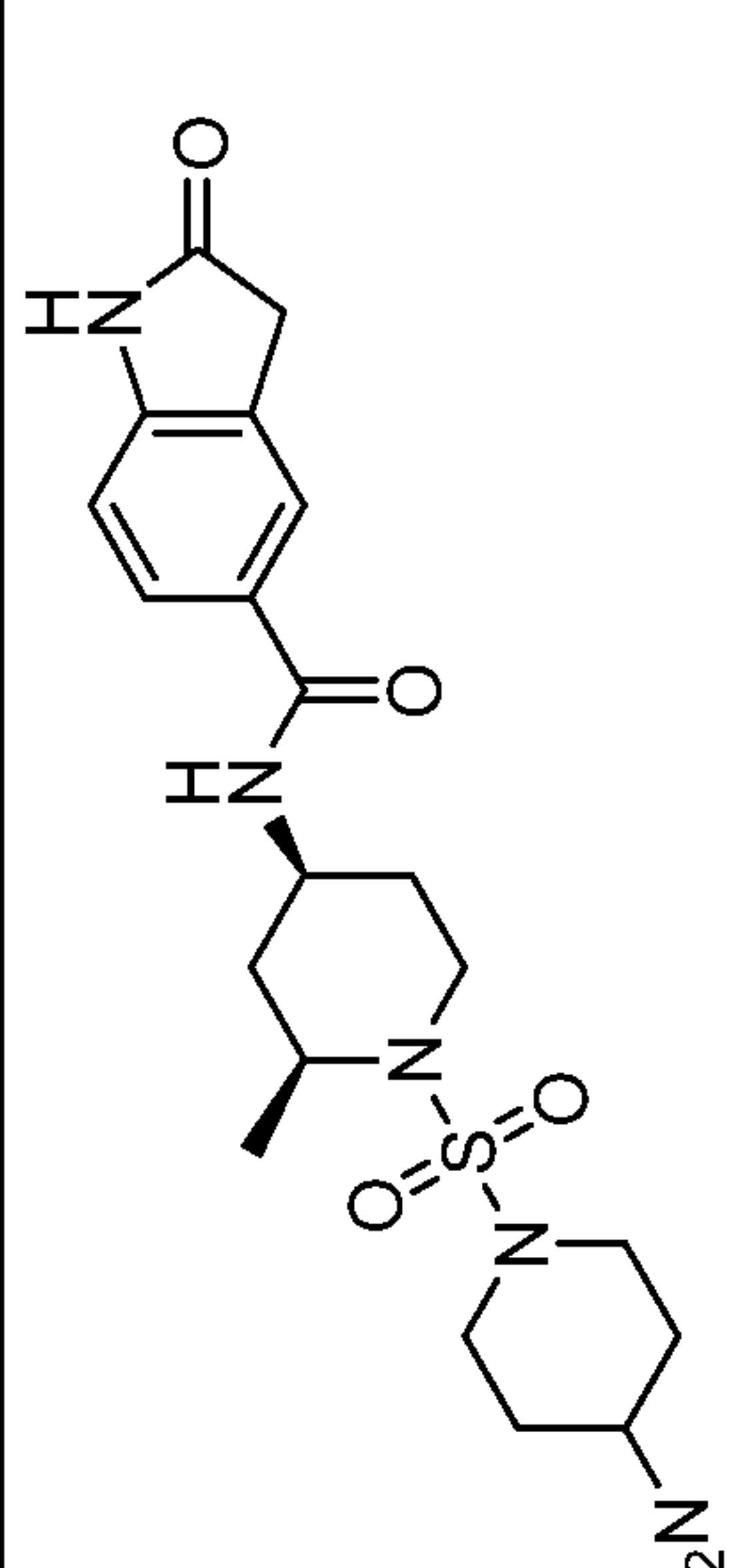
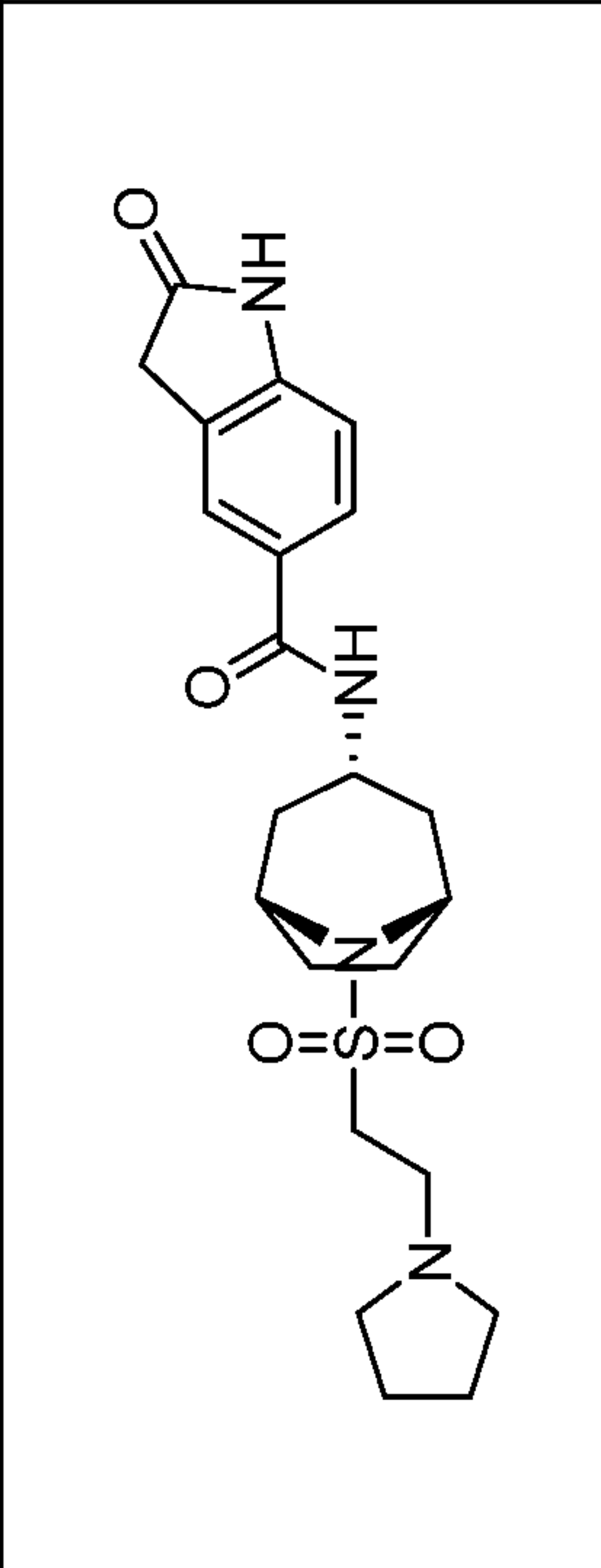
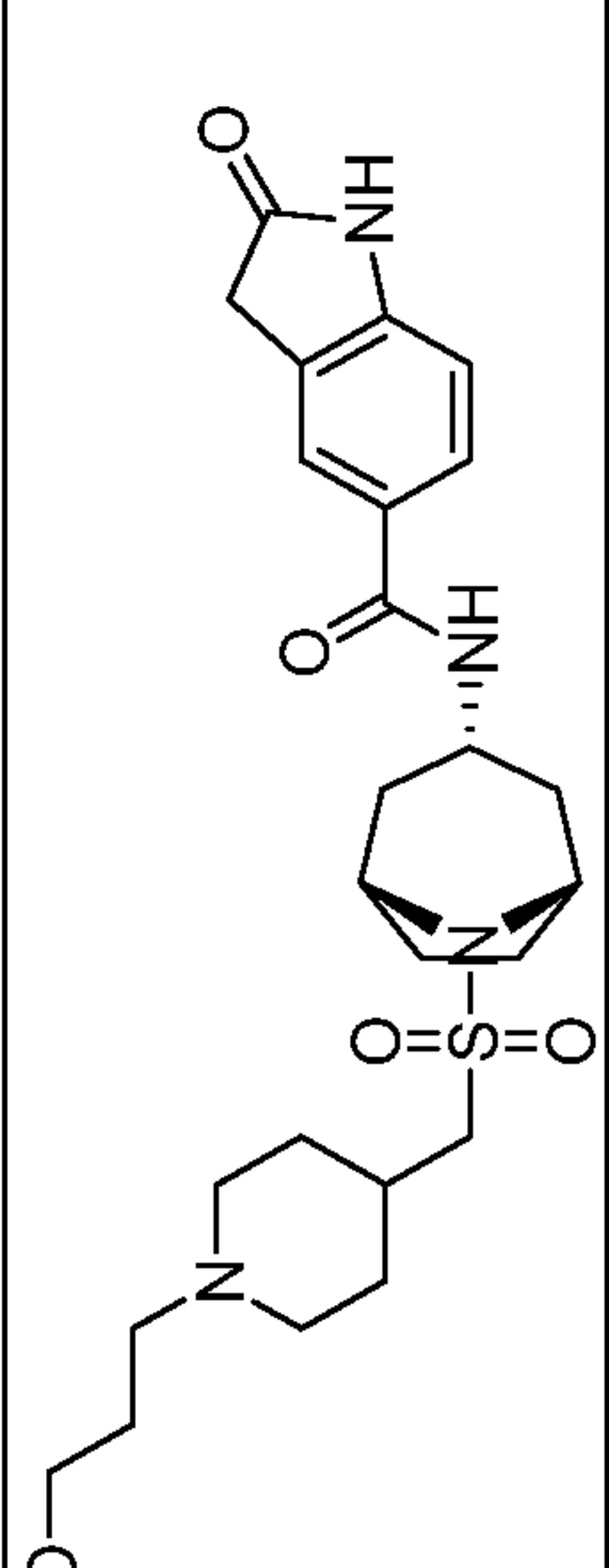
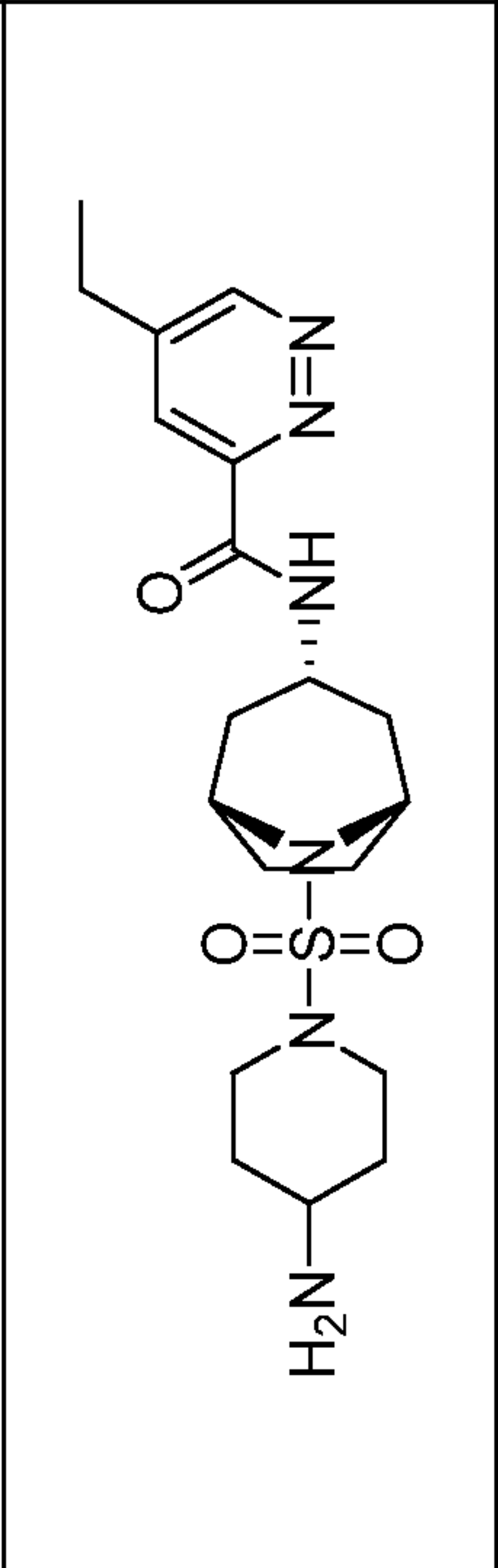
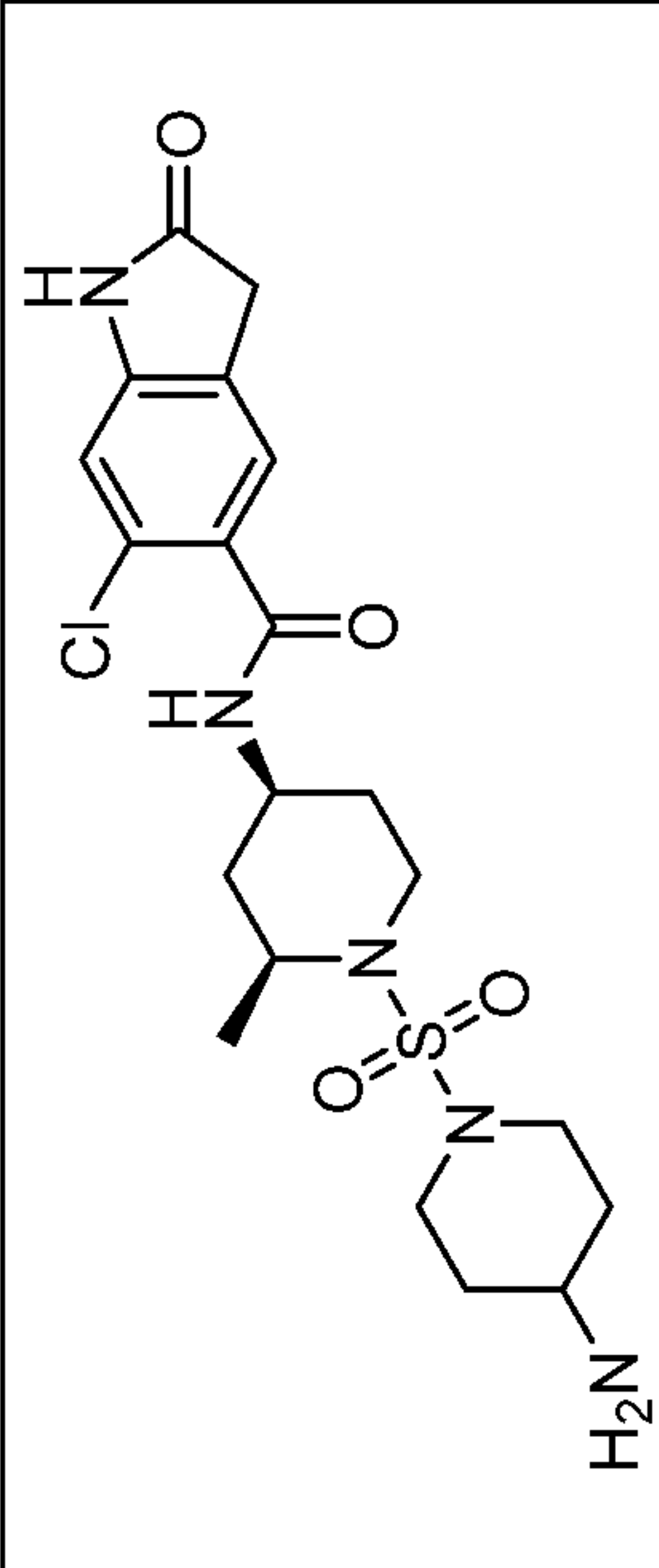
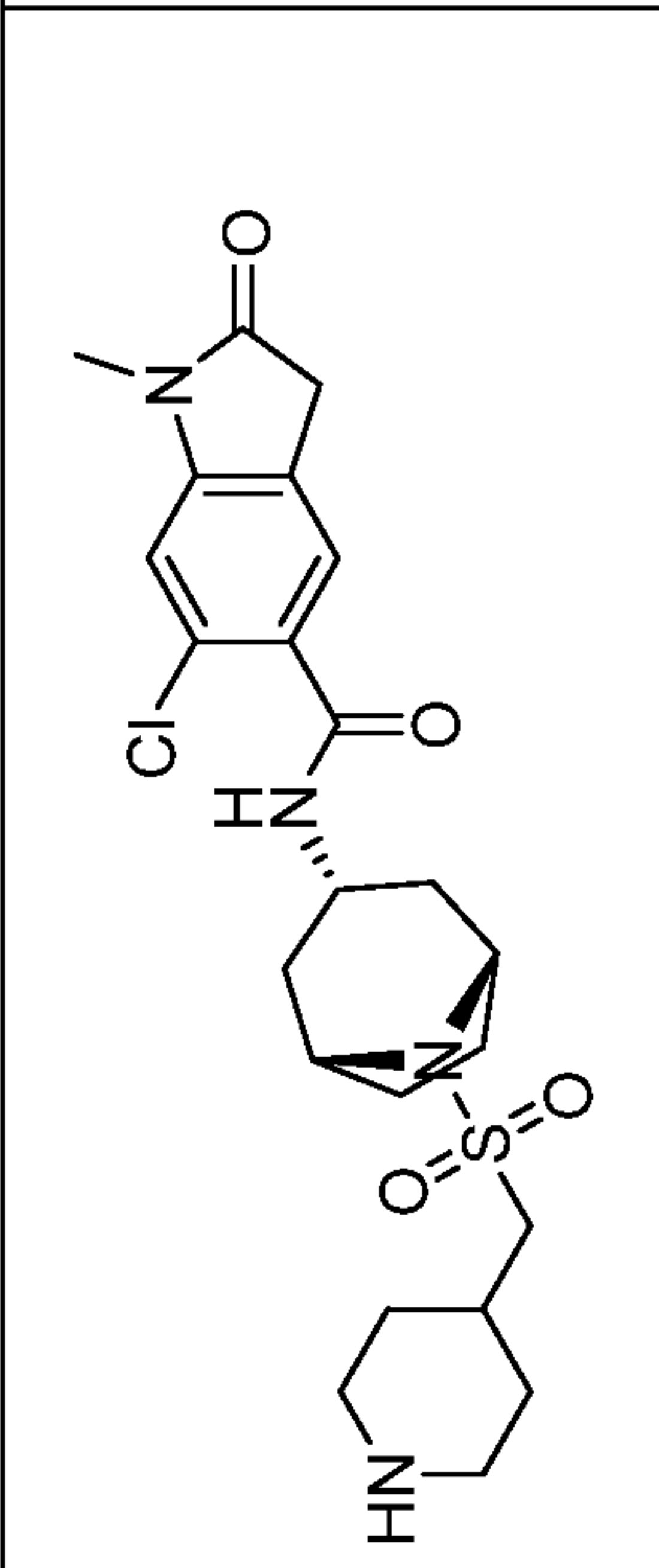
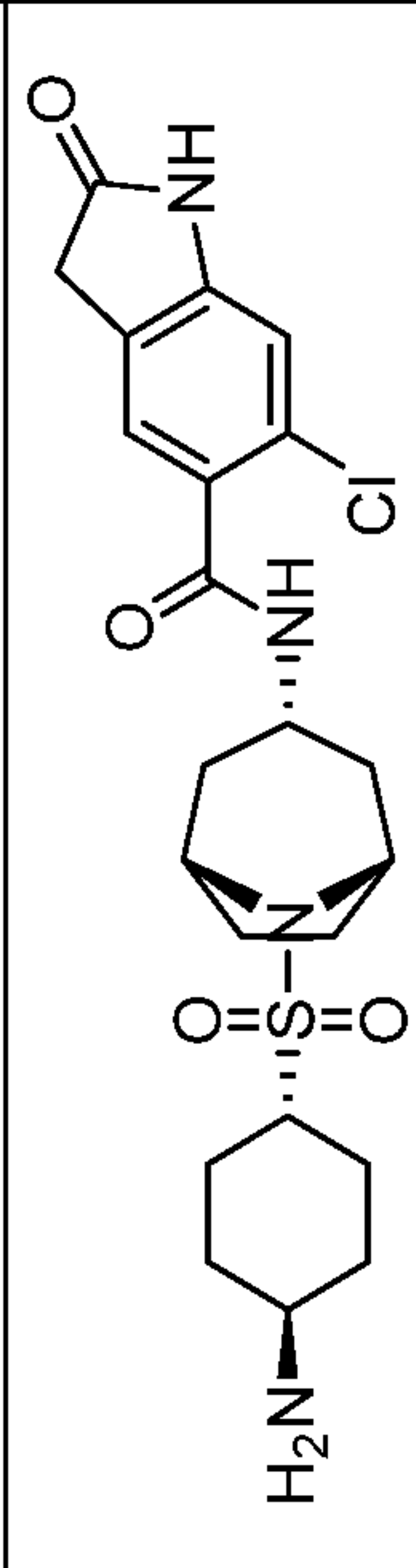
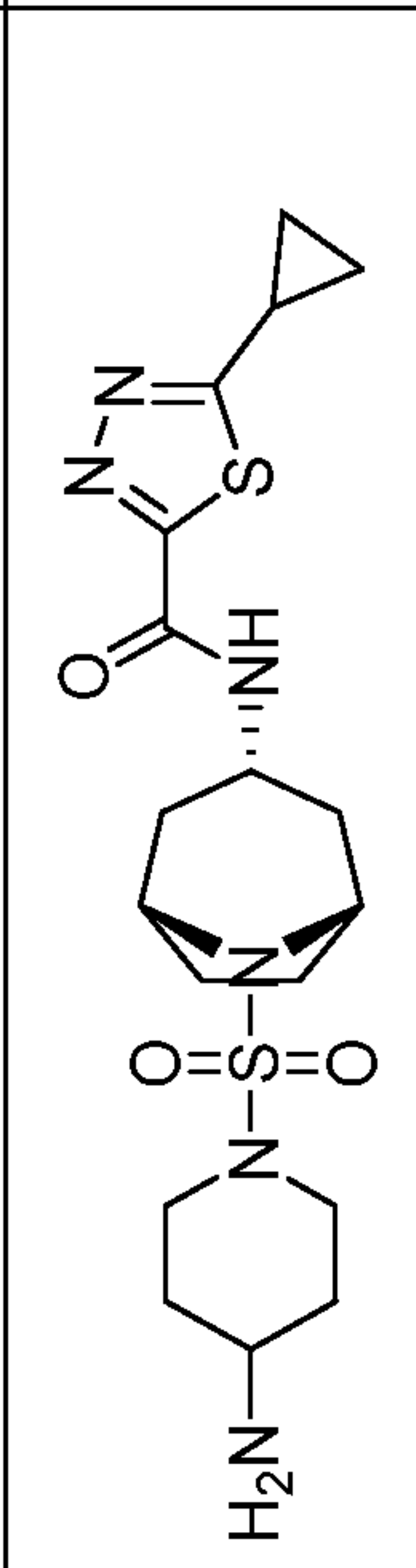
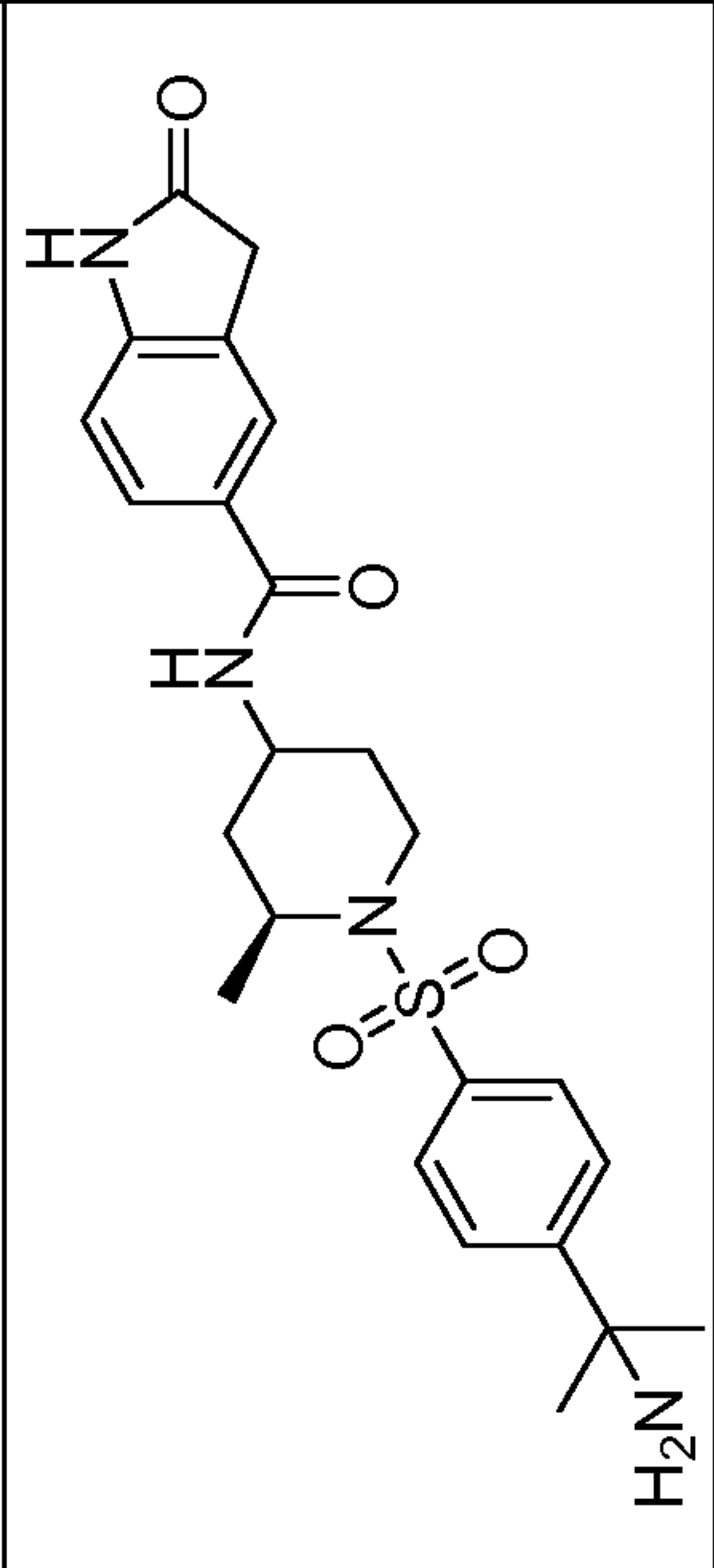
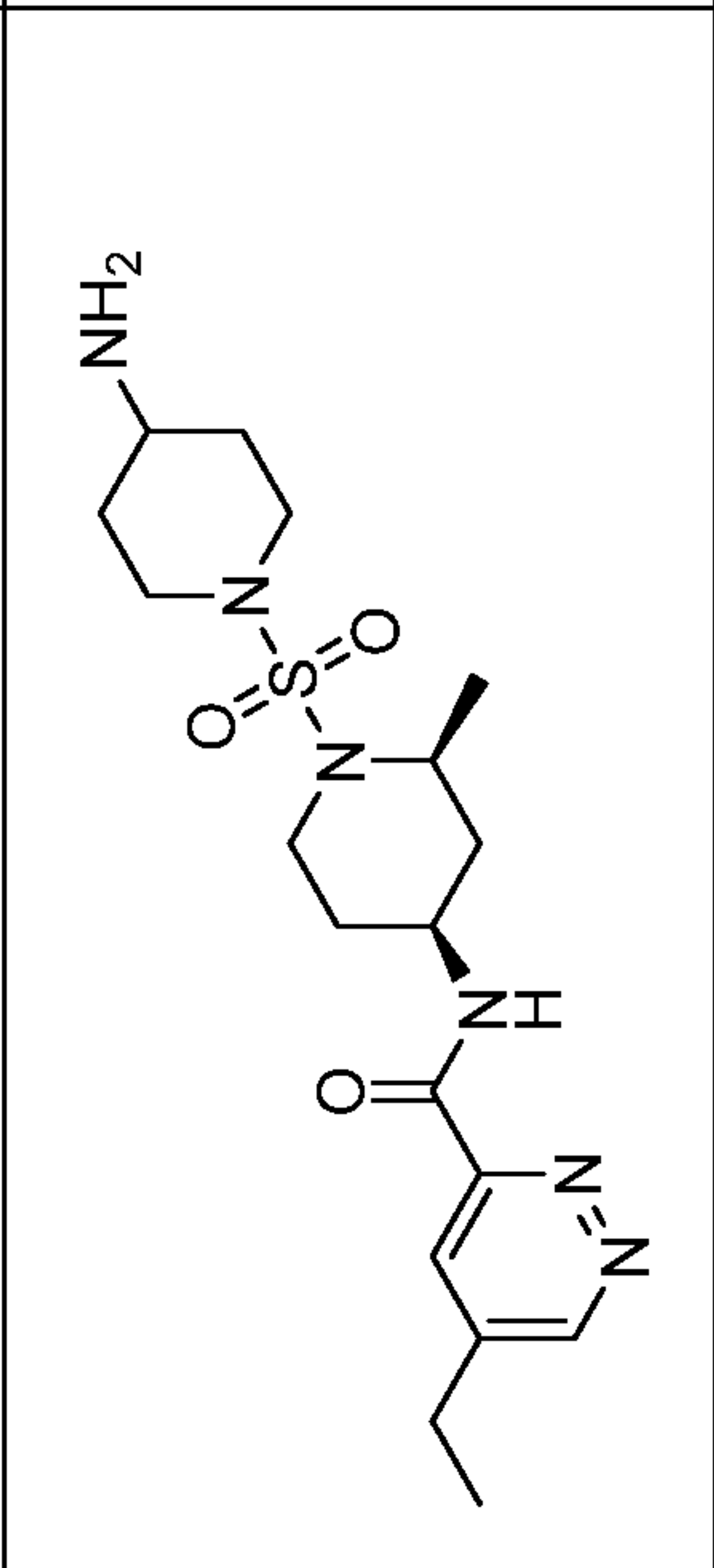
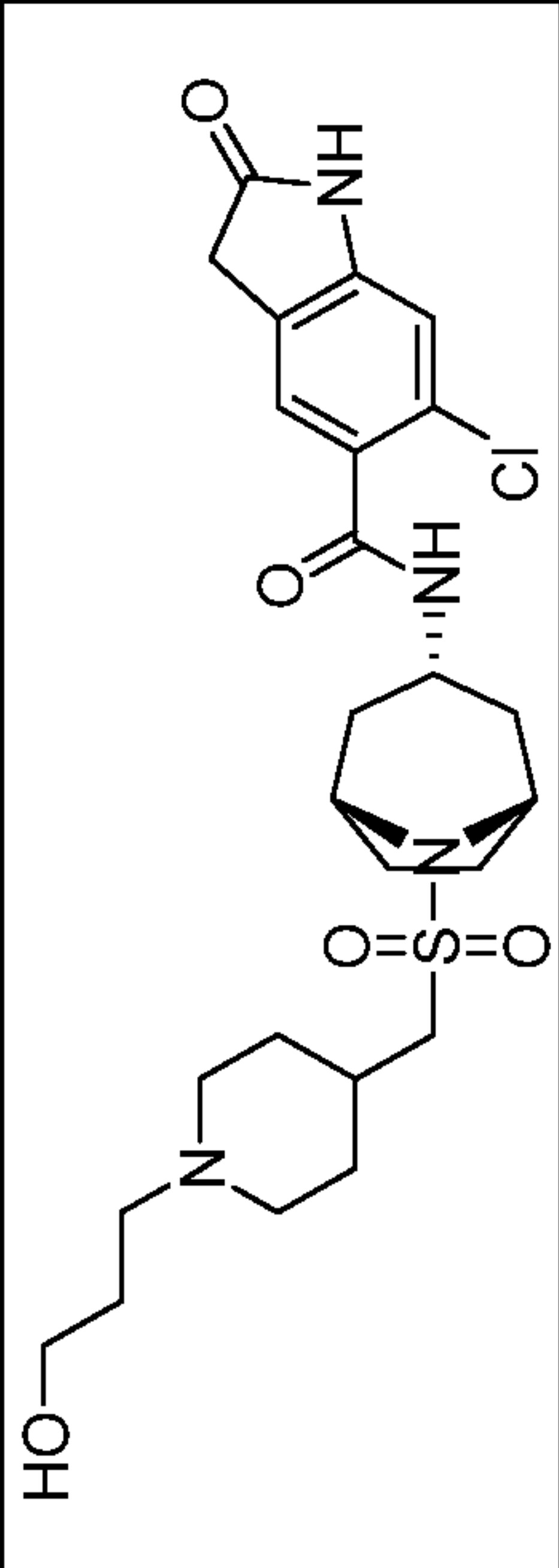
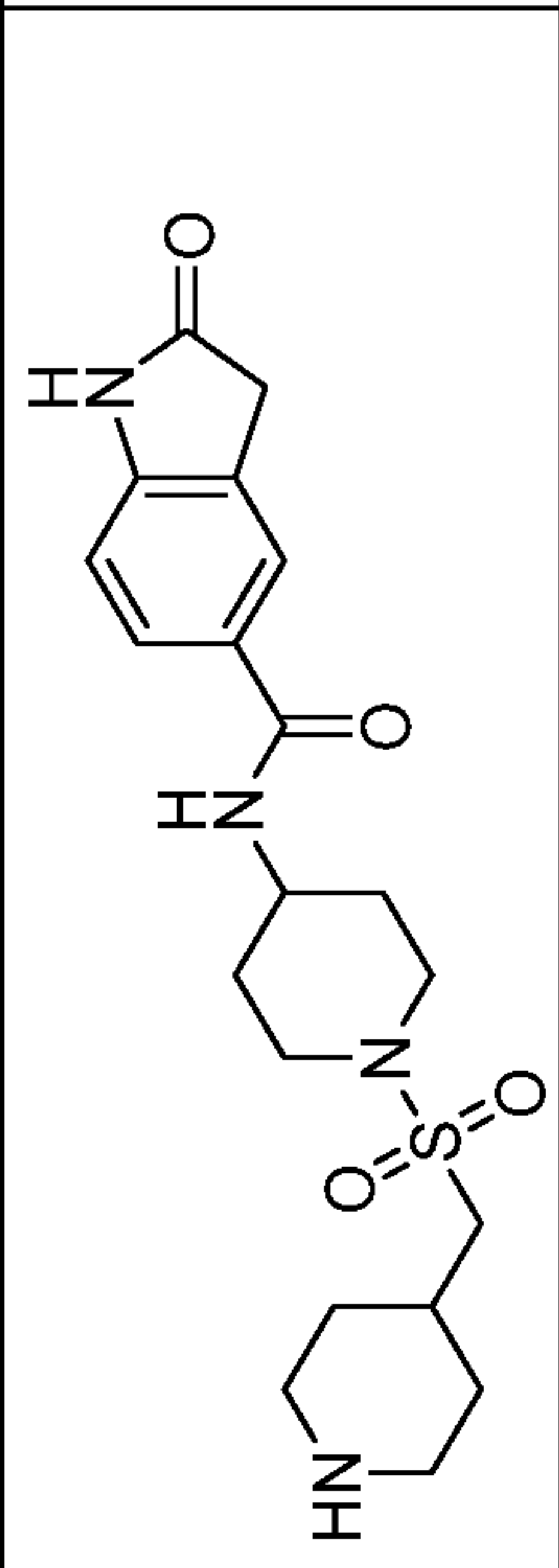
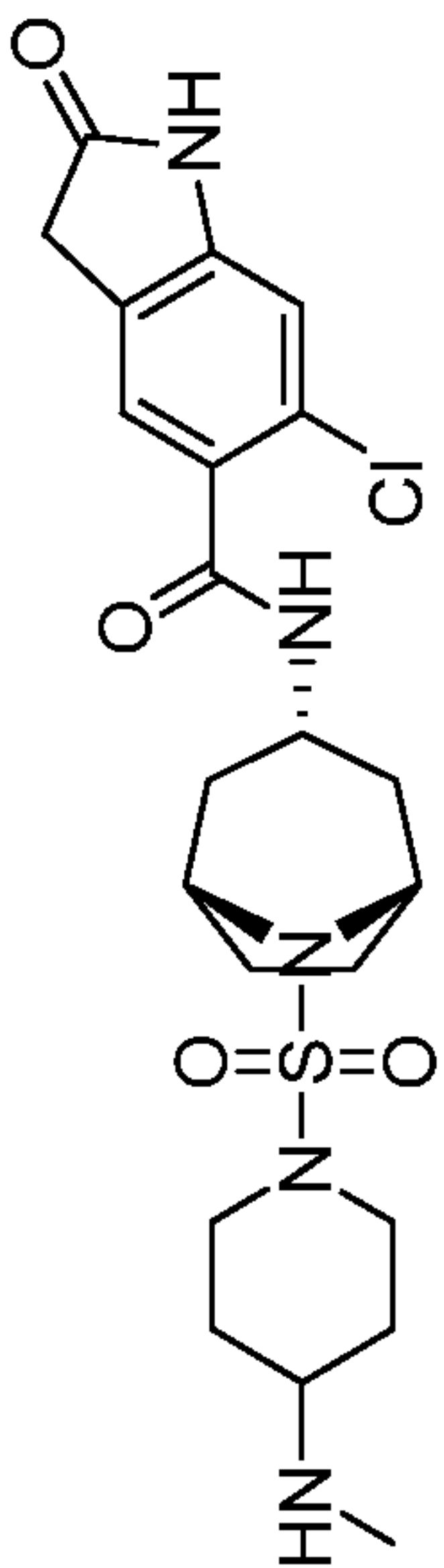
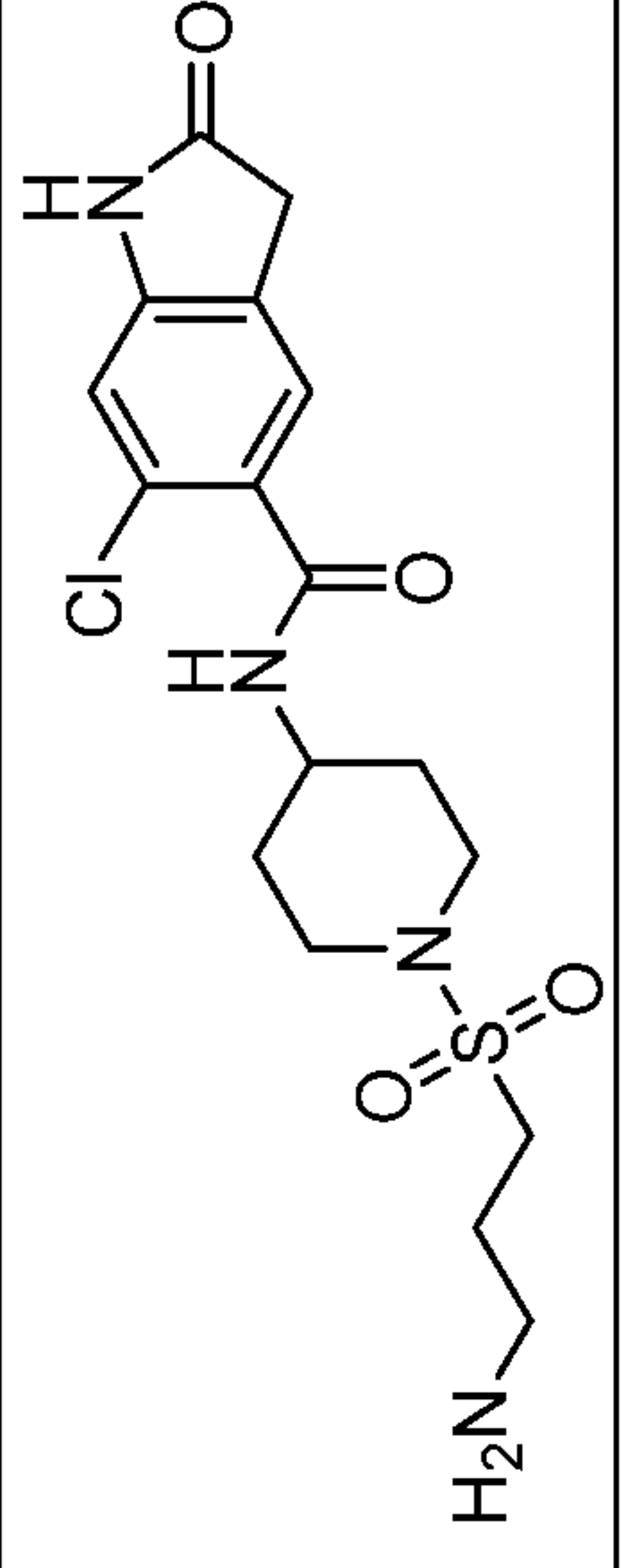
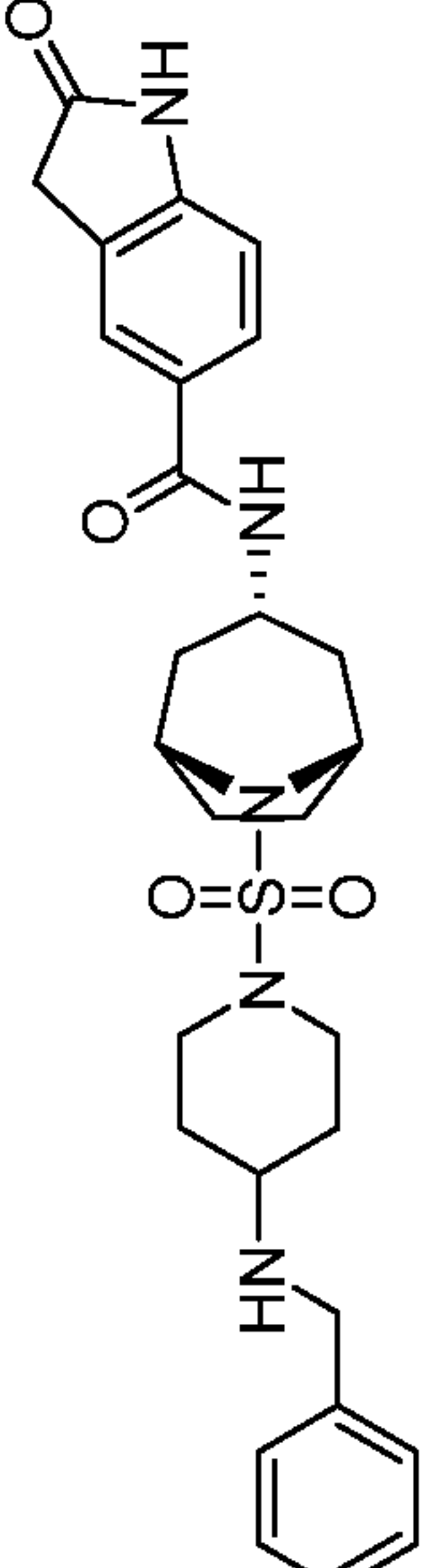
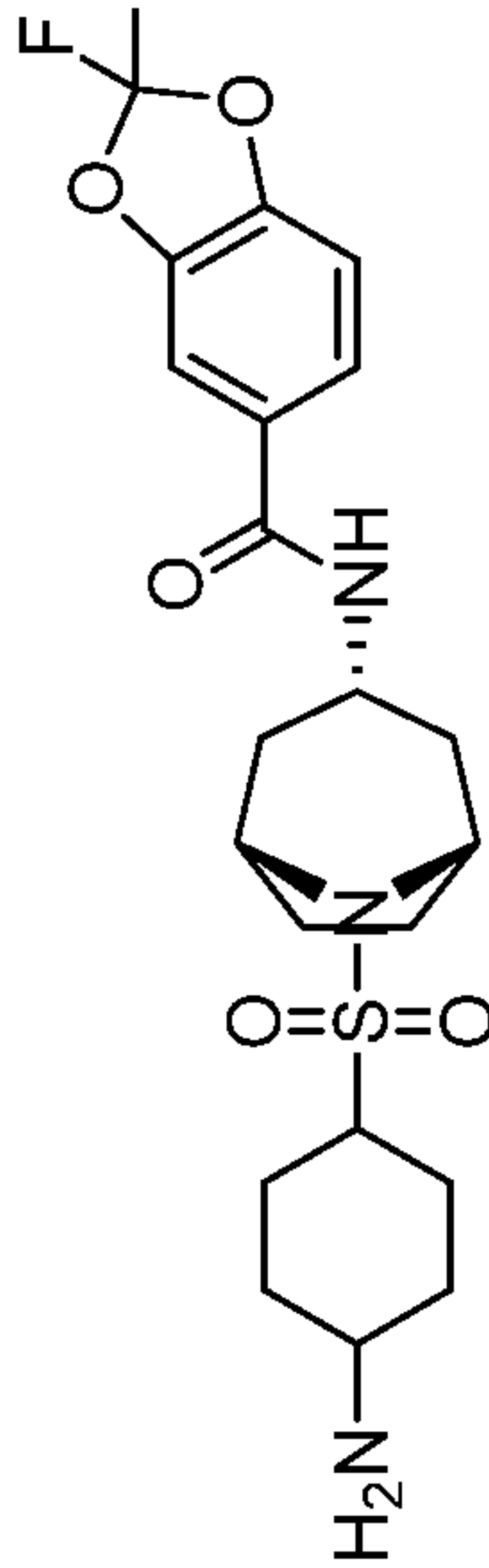
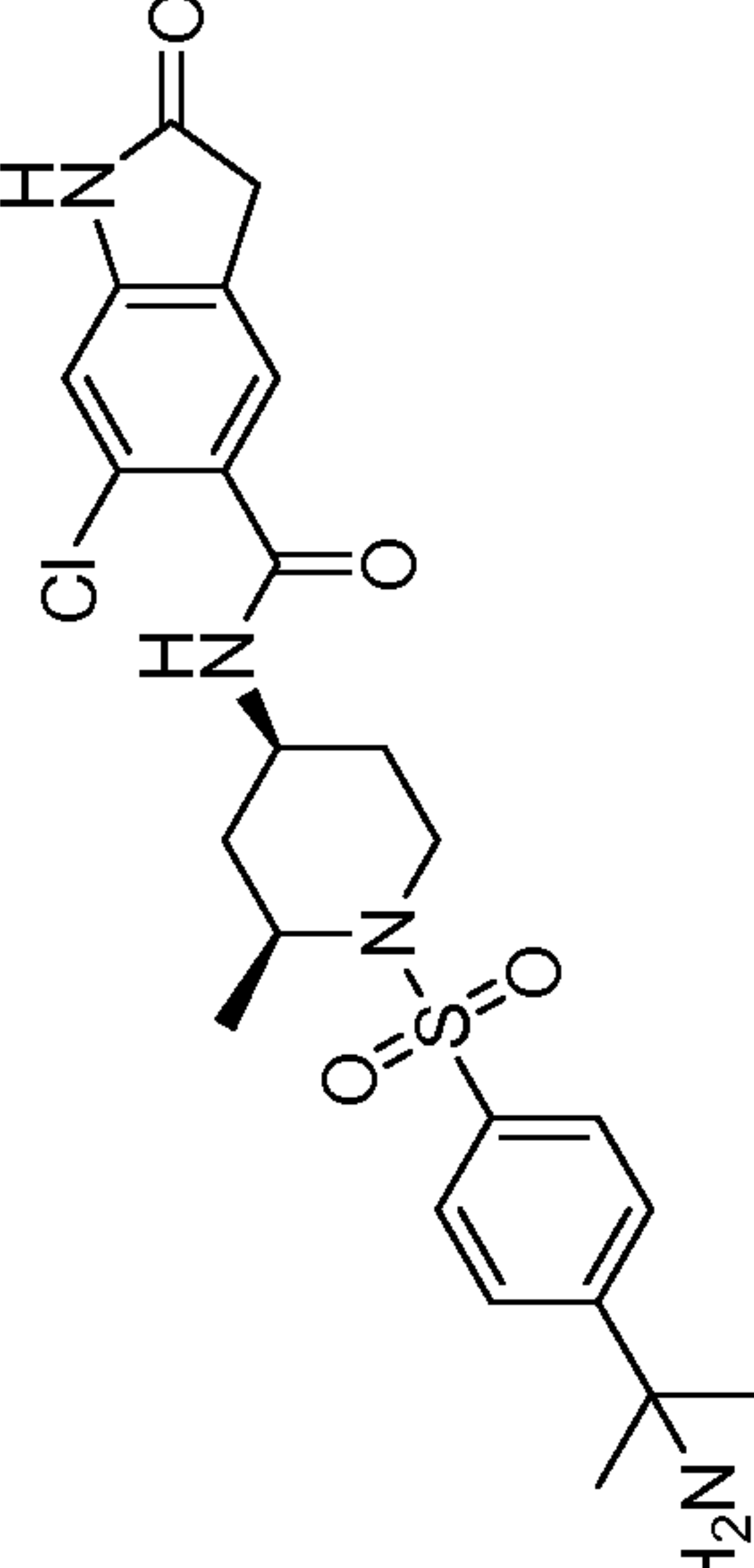
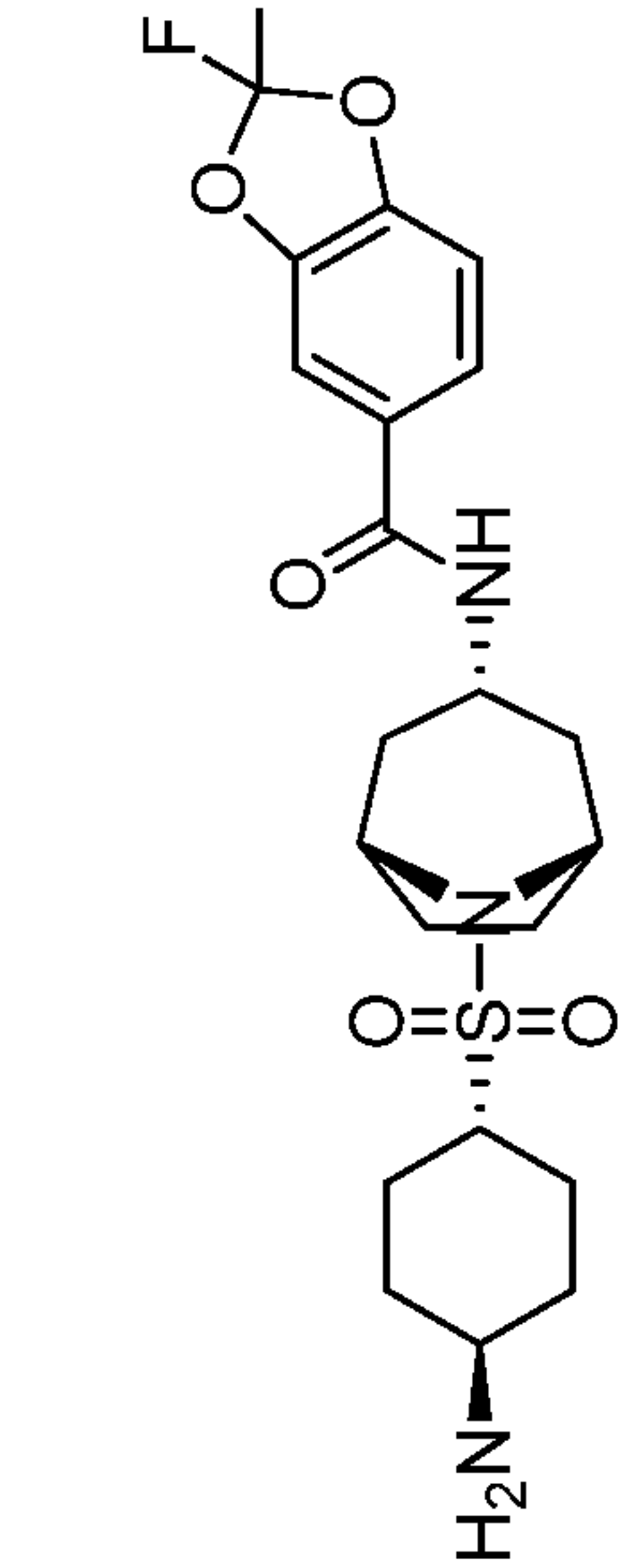
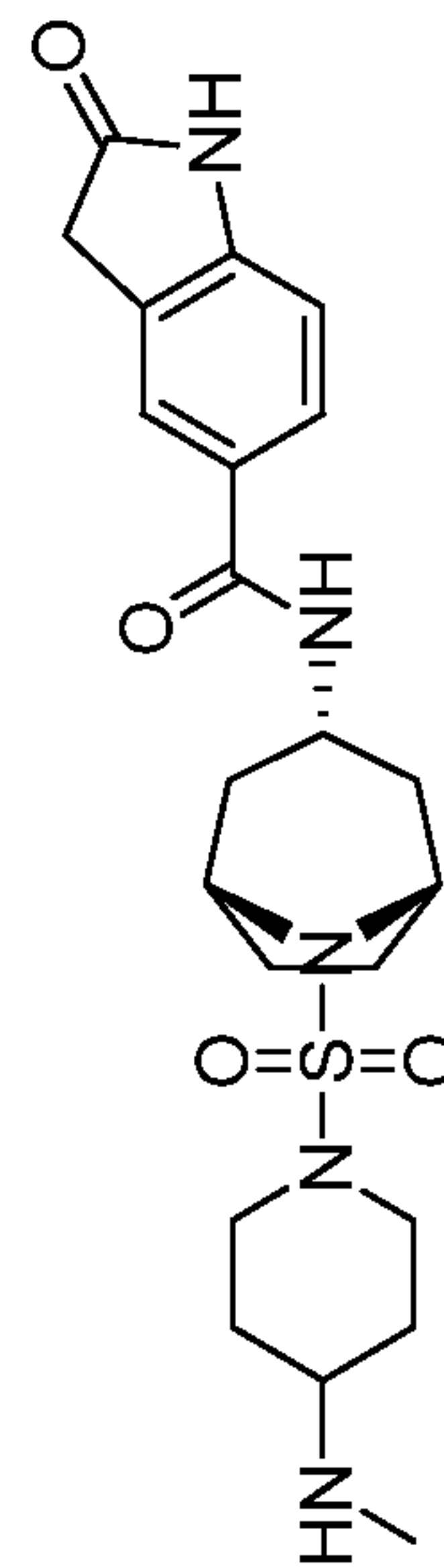
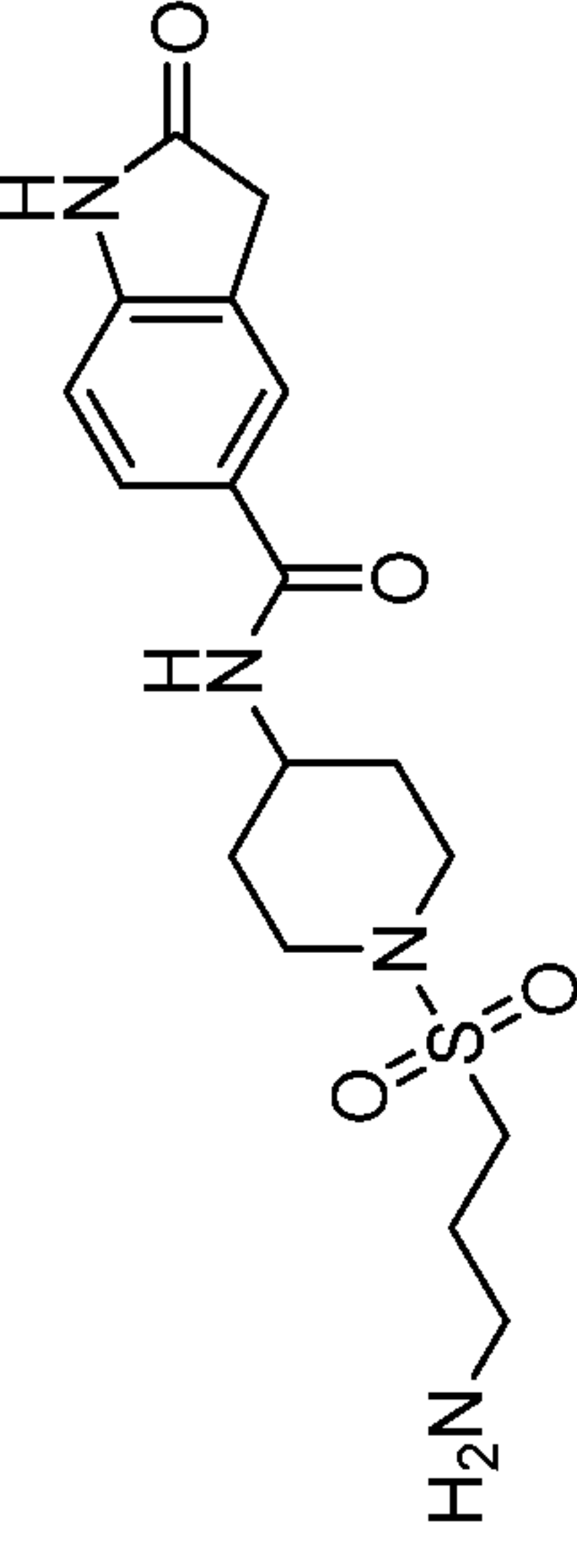
289		None	574		TFA

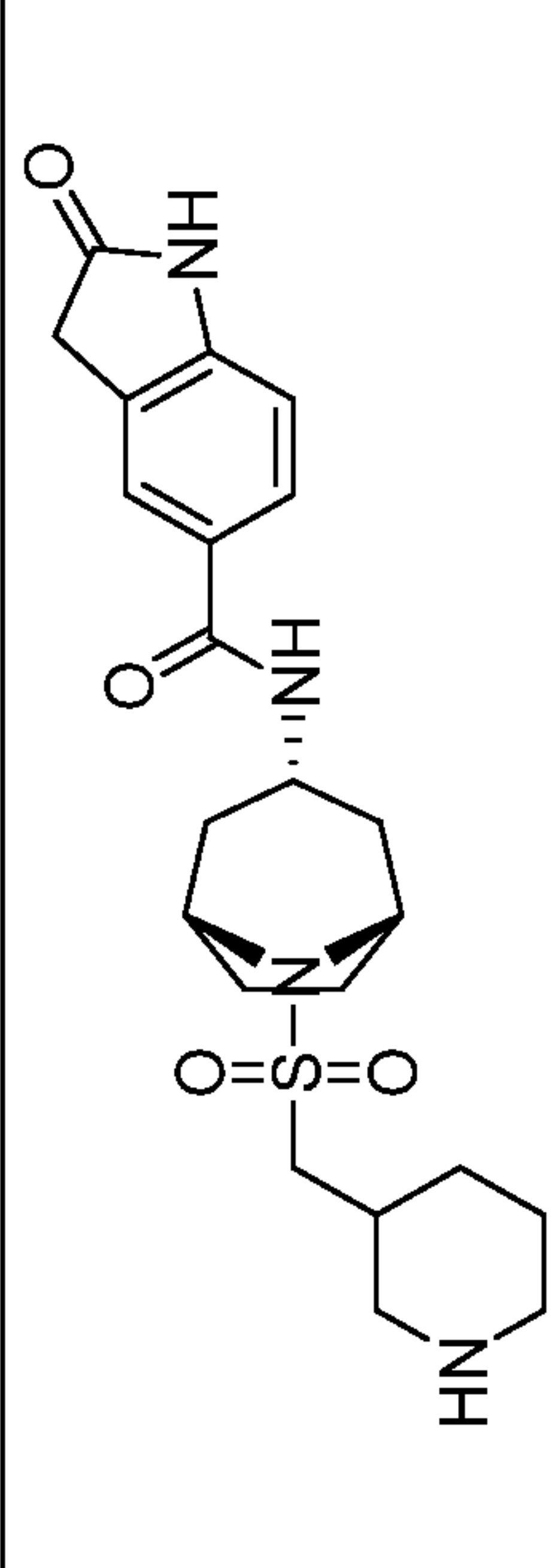
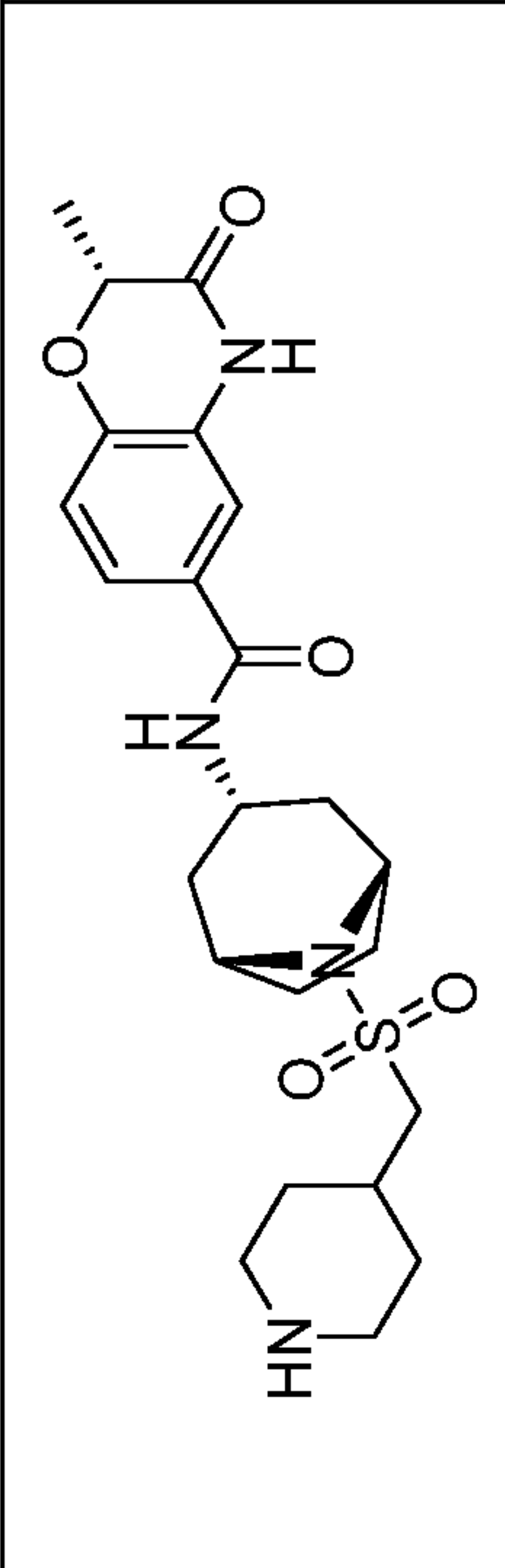
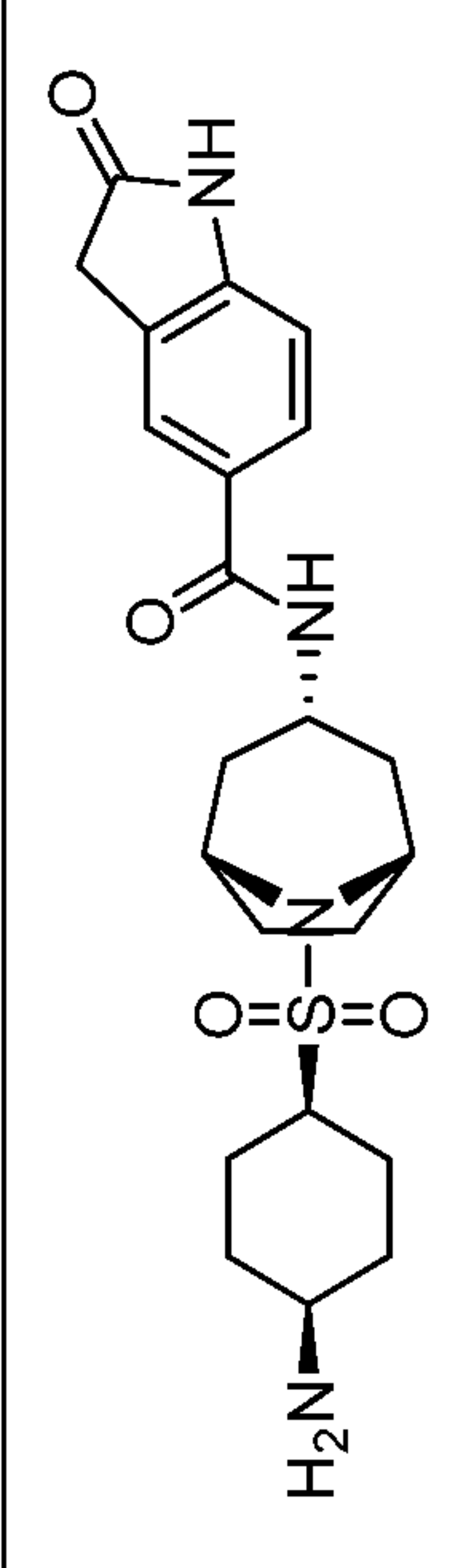
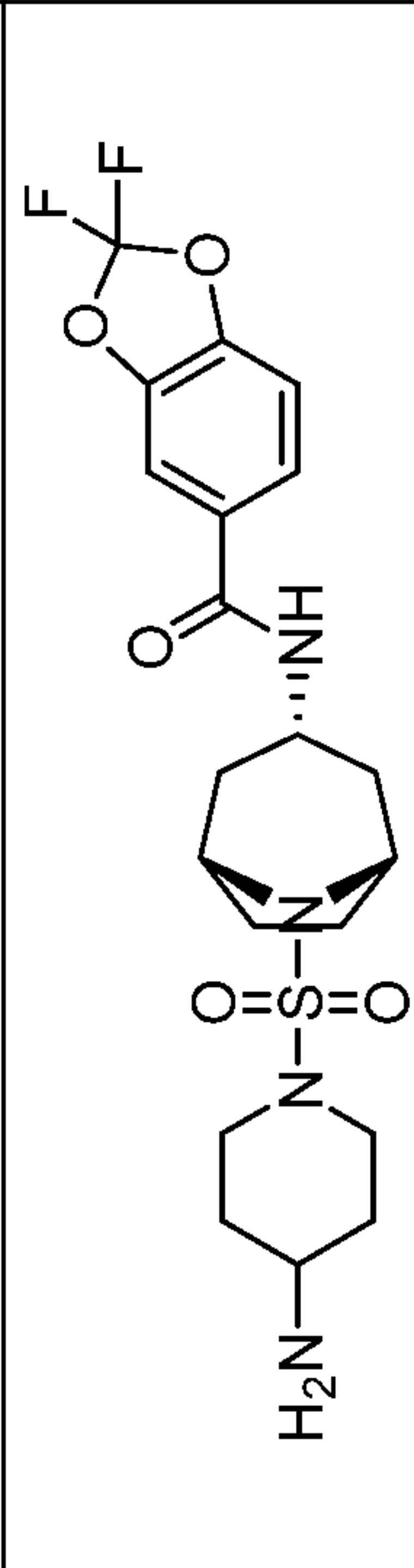
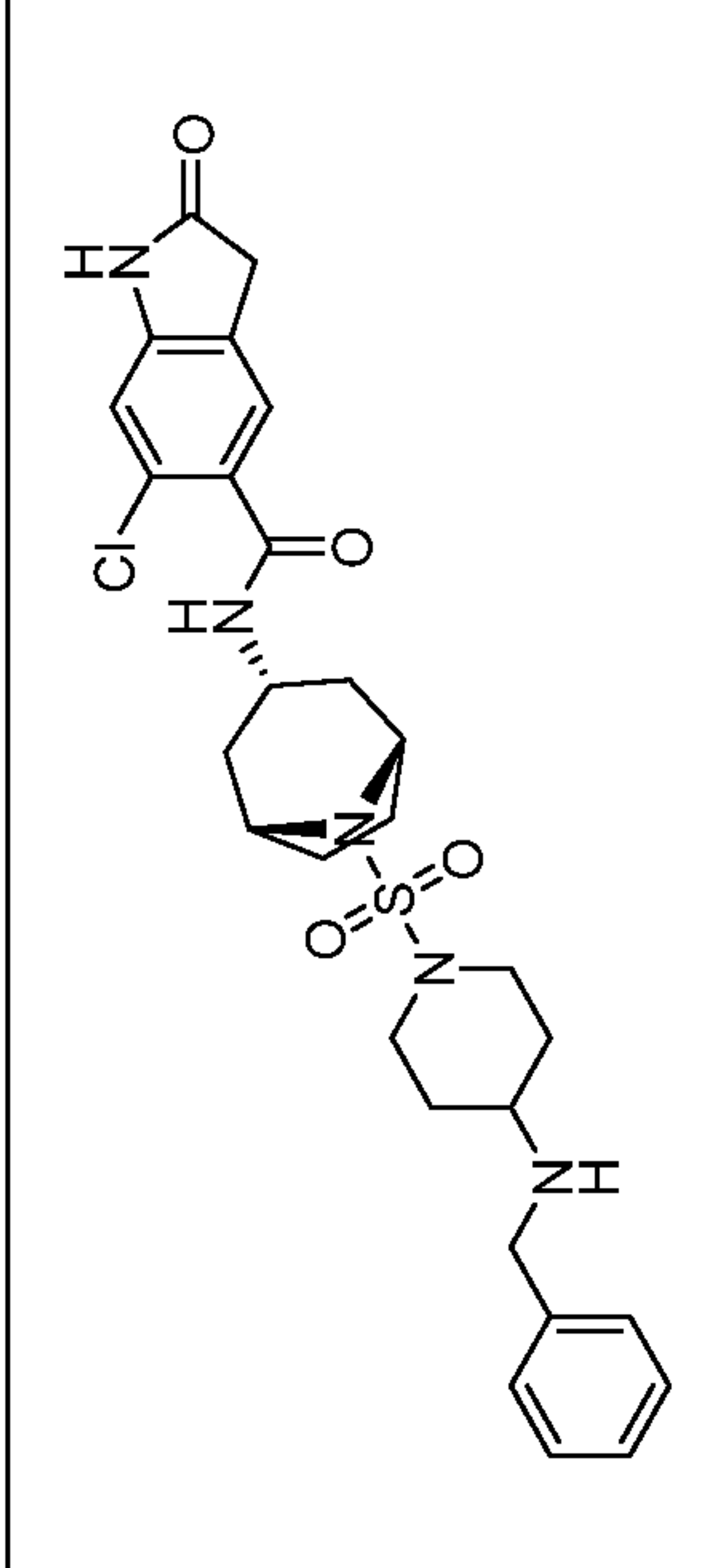
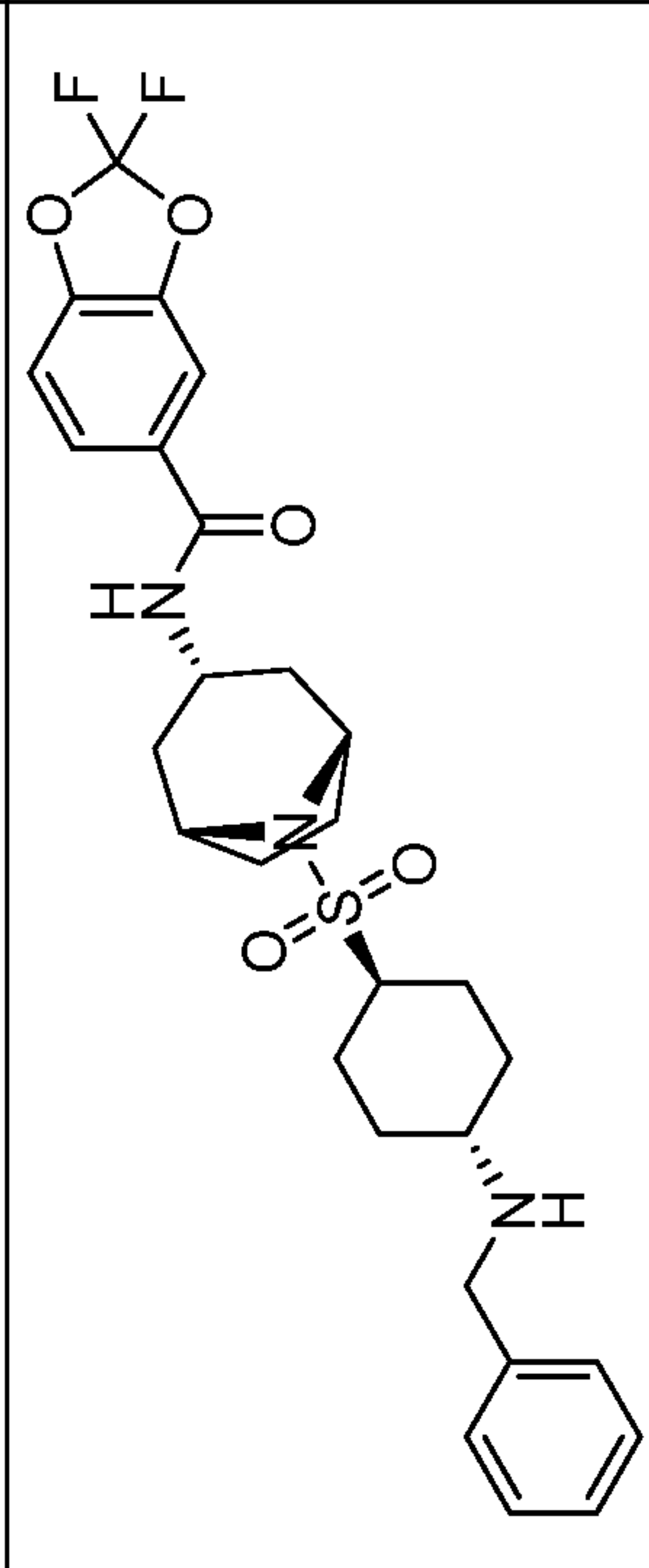
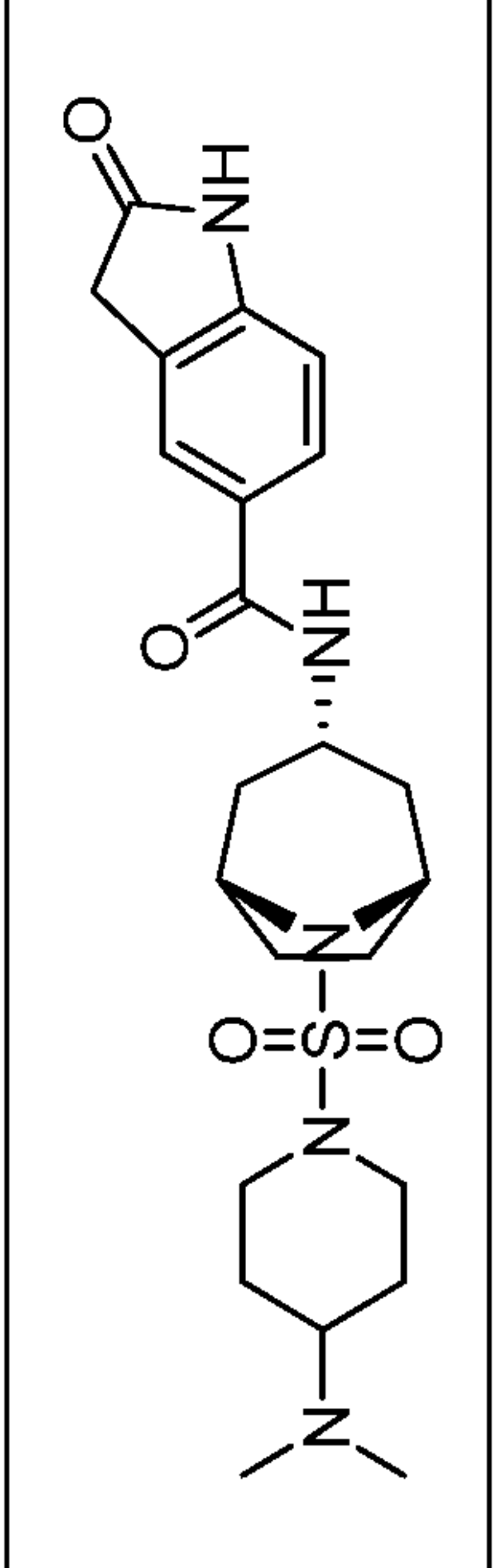
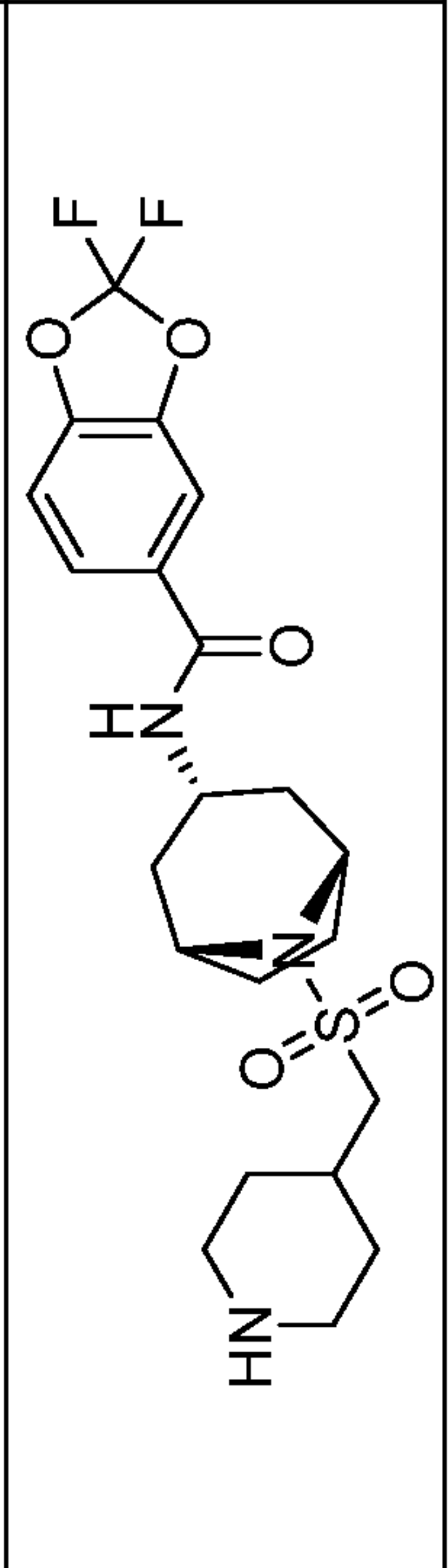
Table 3

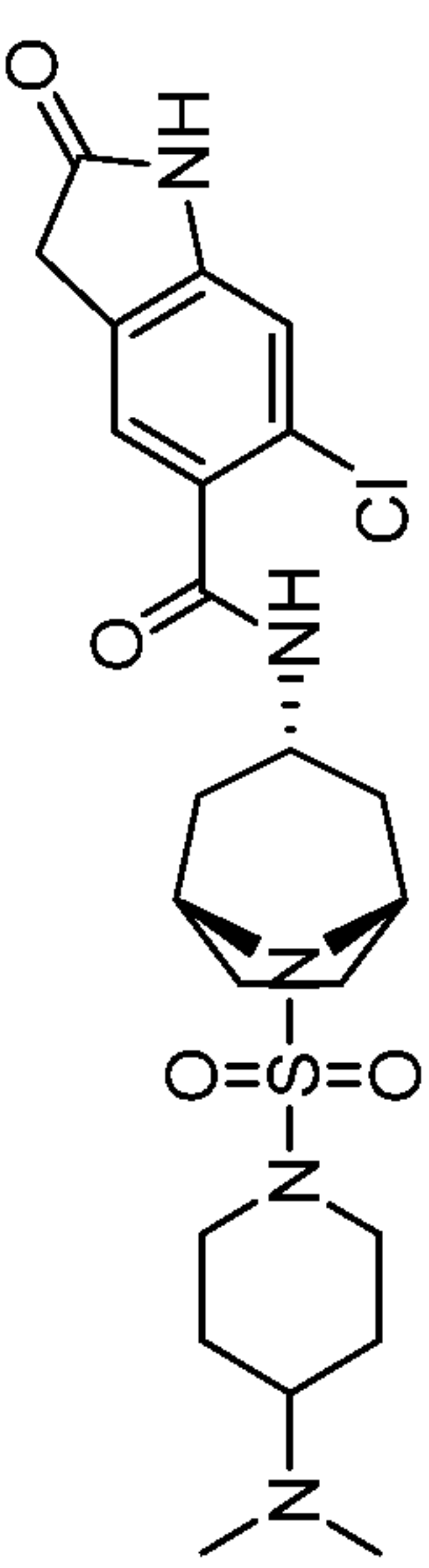
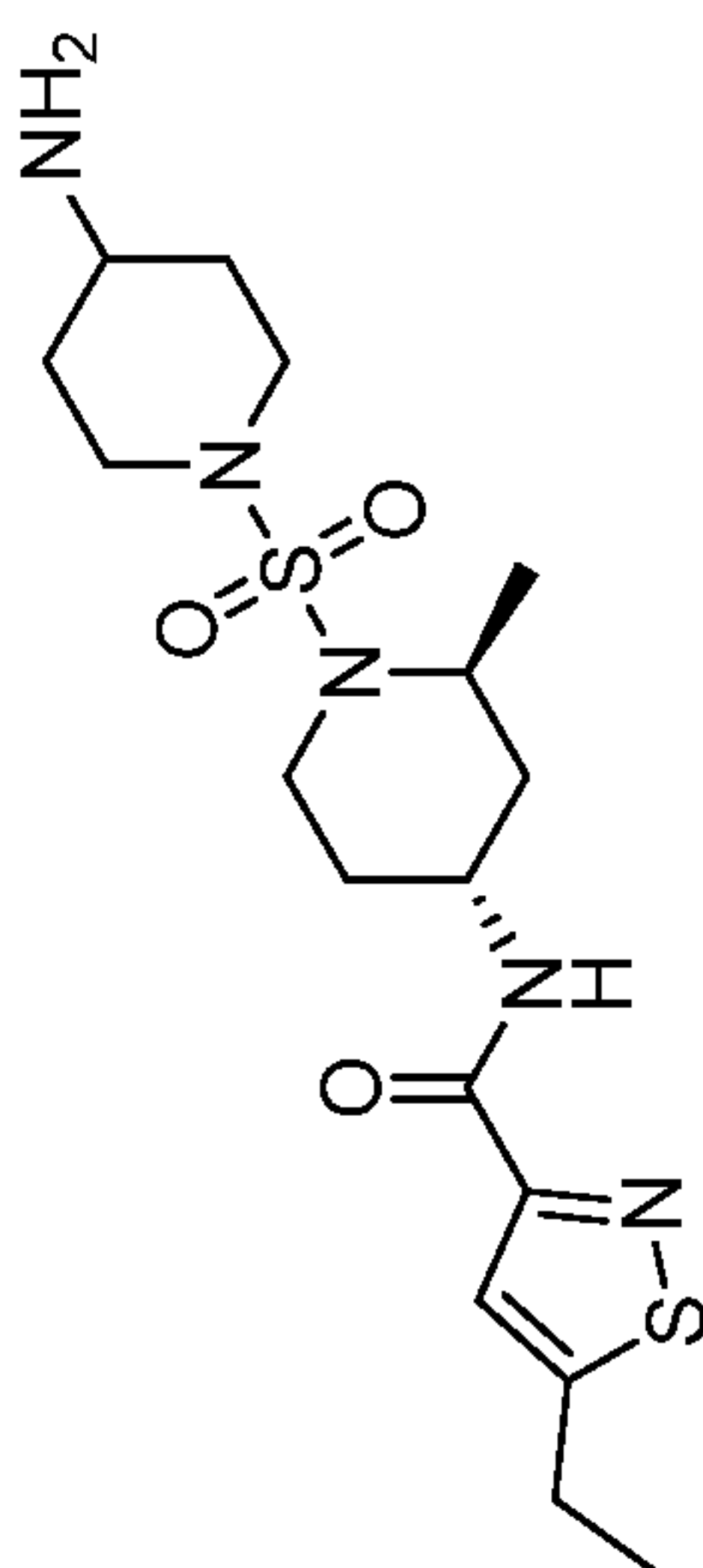
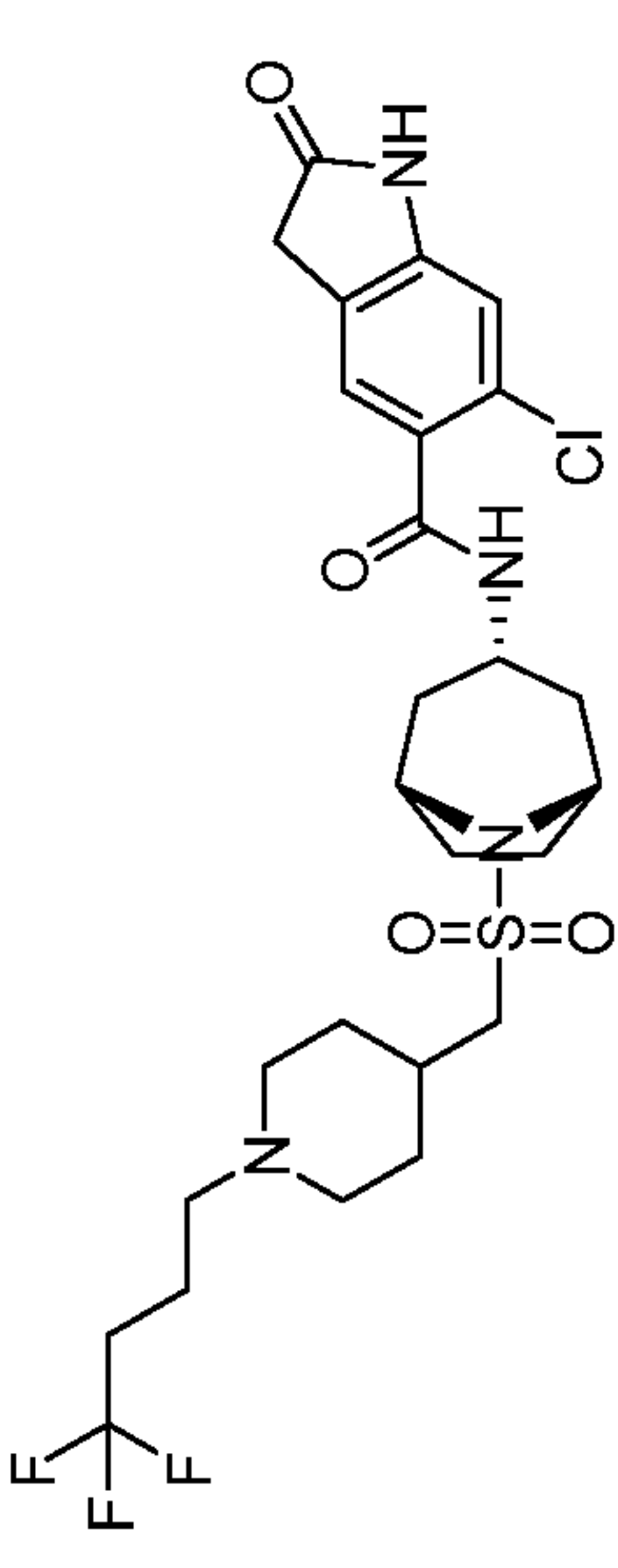
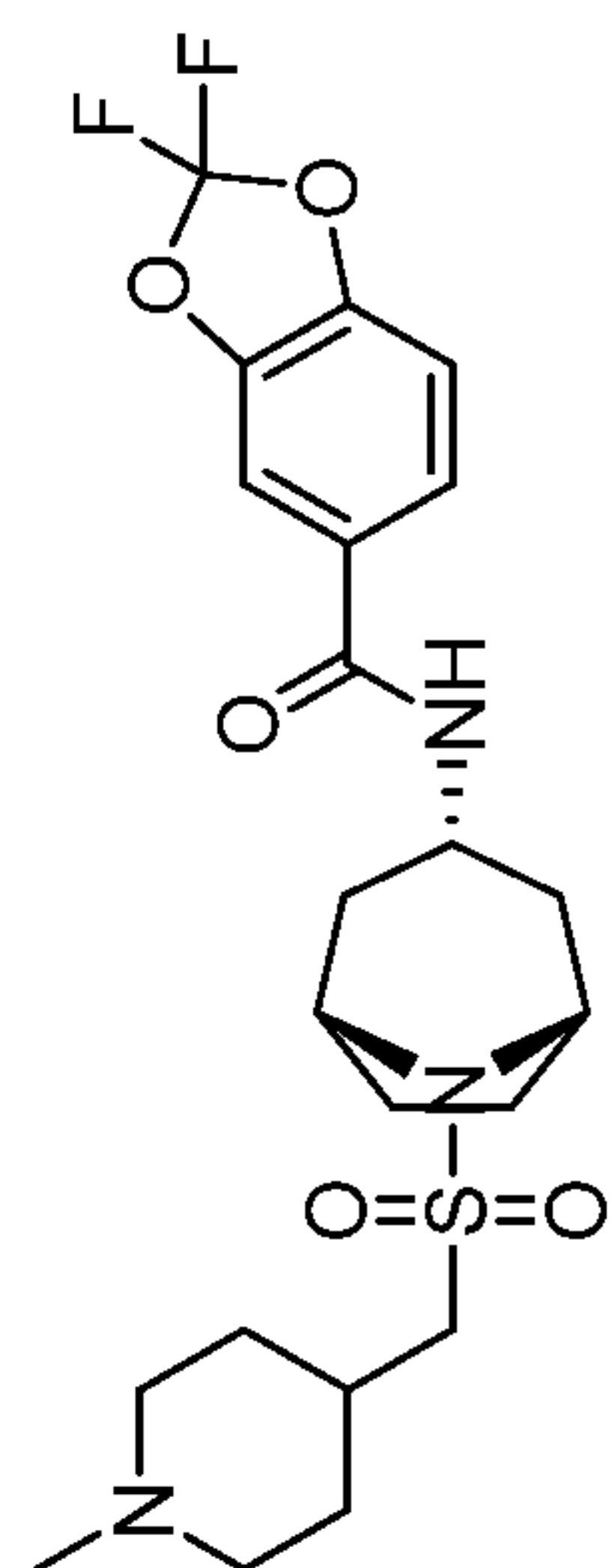
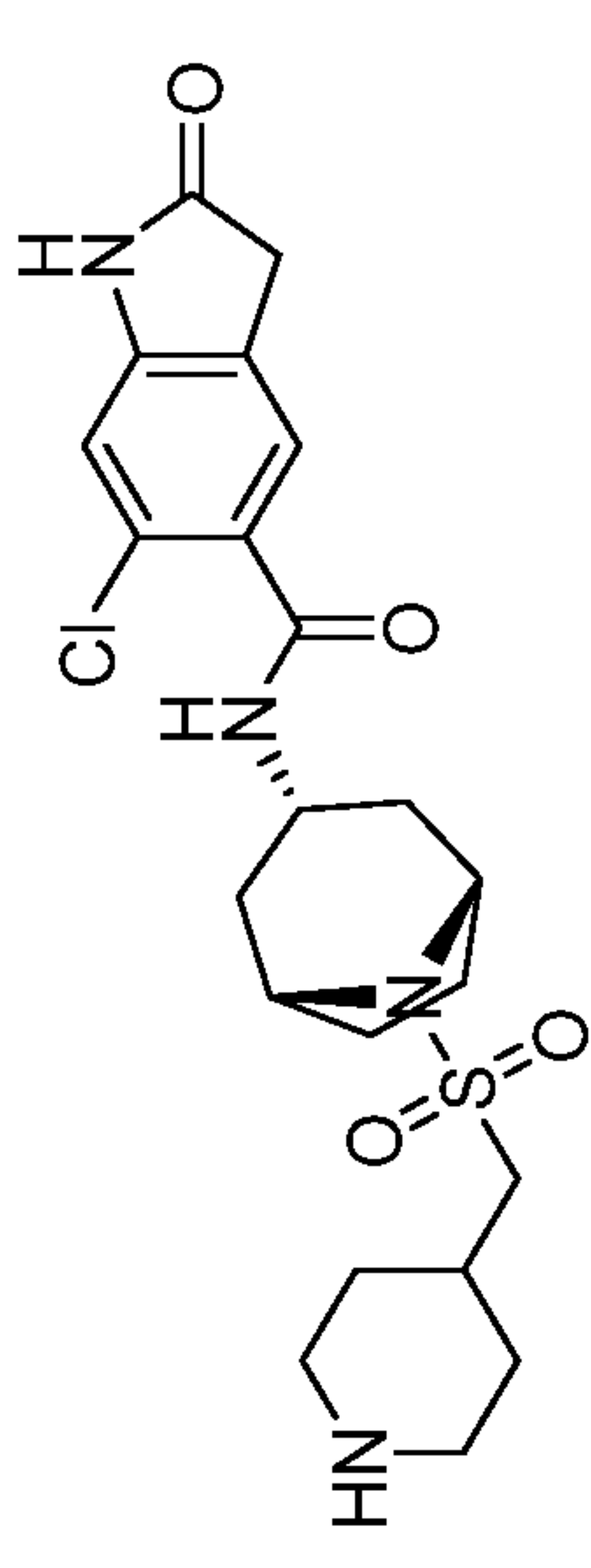
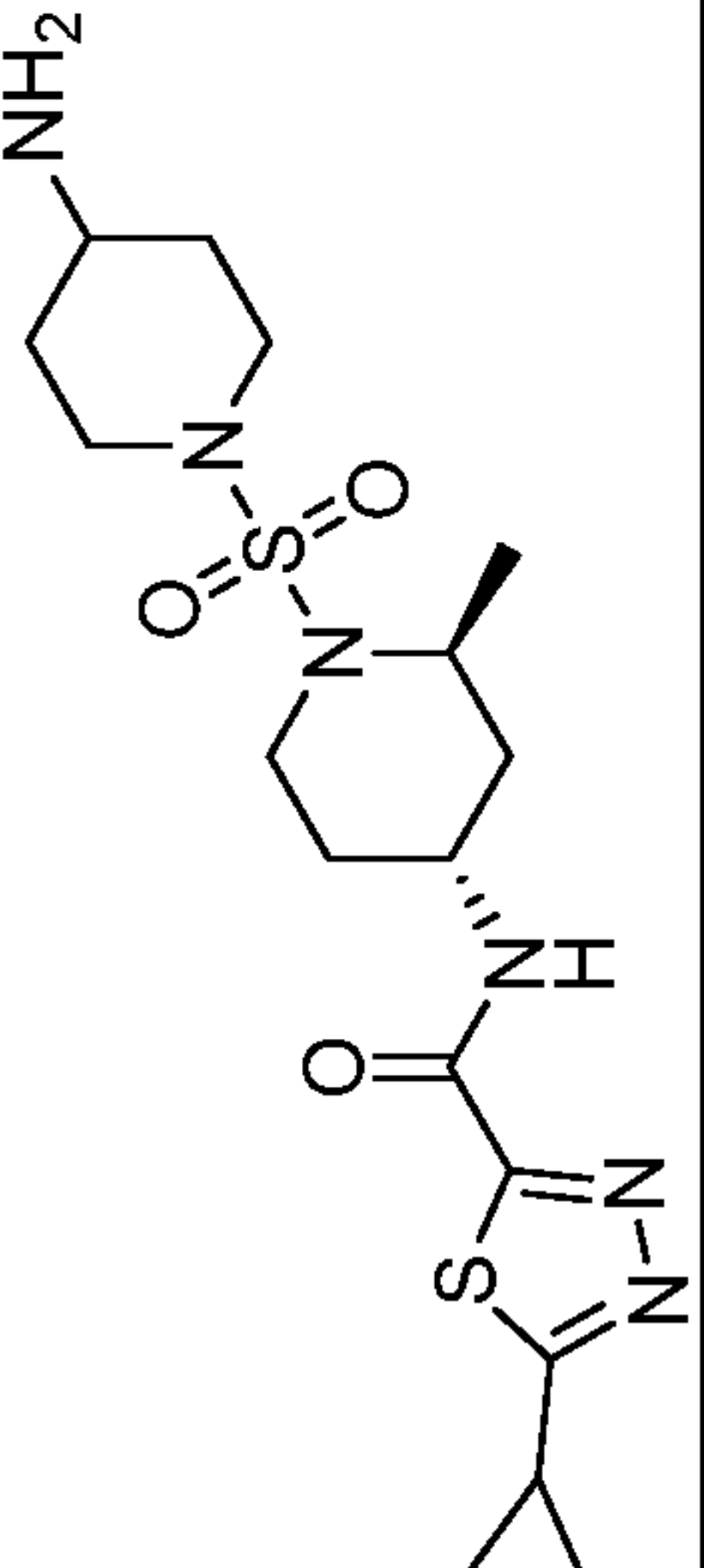
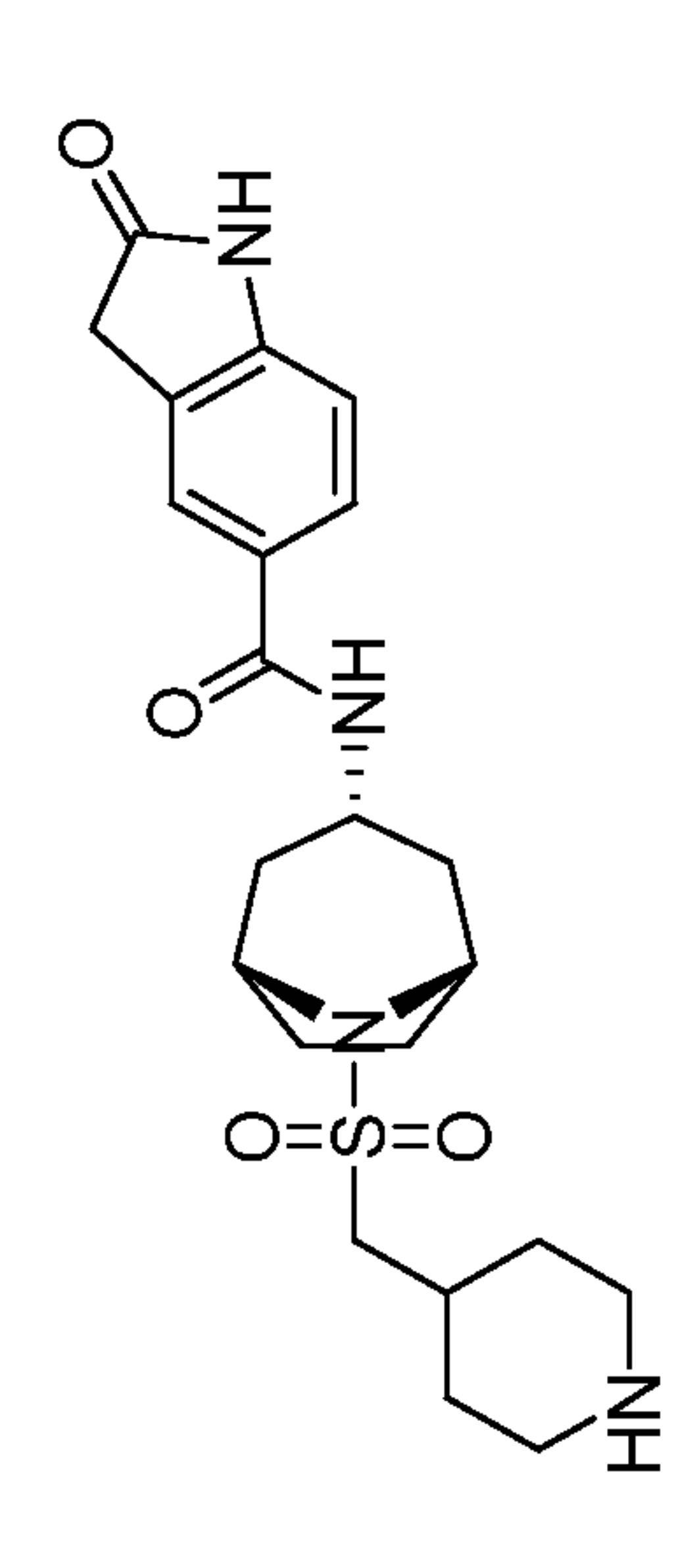
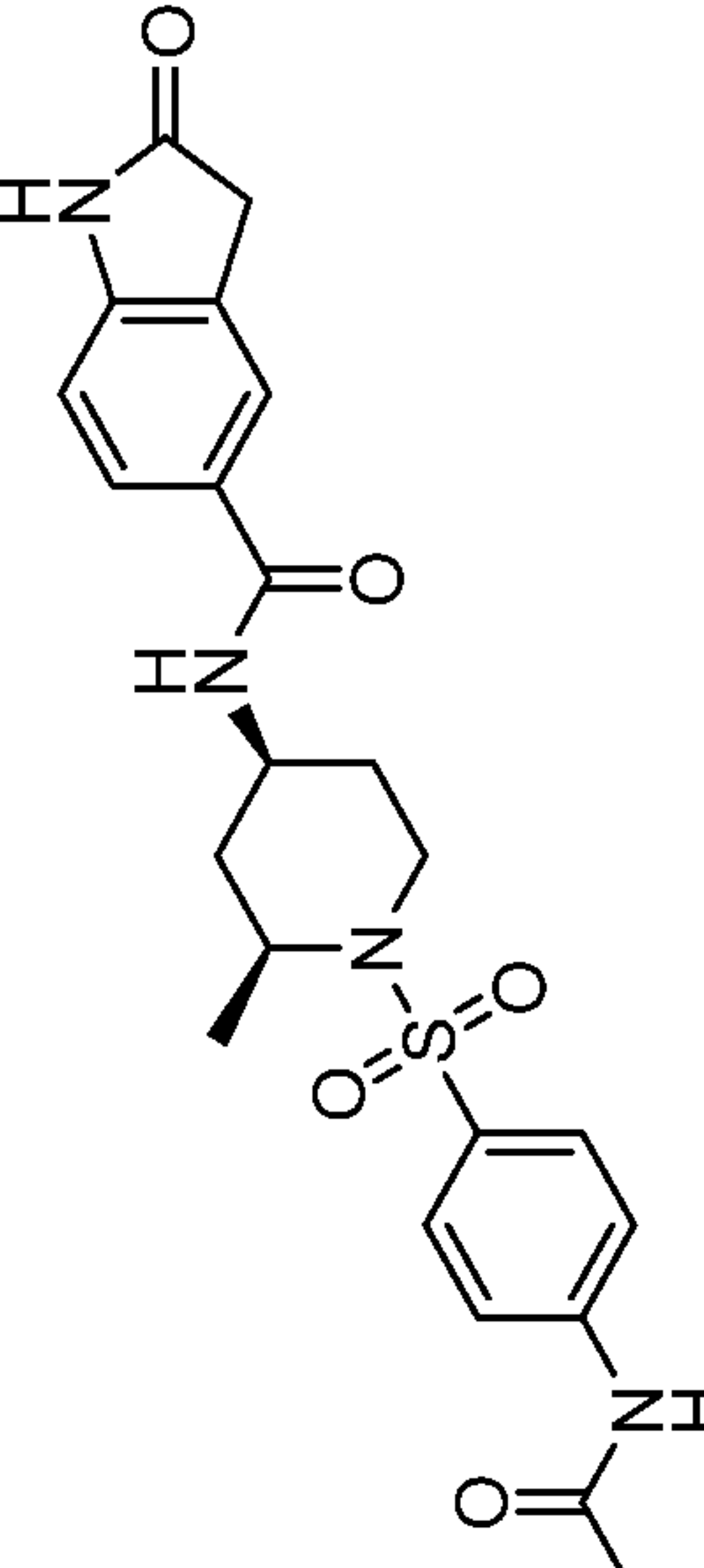
Cpd. No.	Structure	Salt Form	Cpd. No.	Structure	Salt Form
575		TFA	610		HCl
576		None	611		TFA

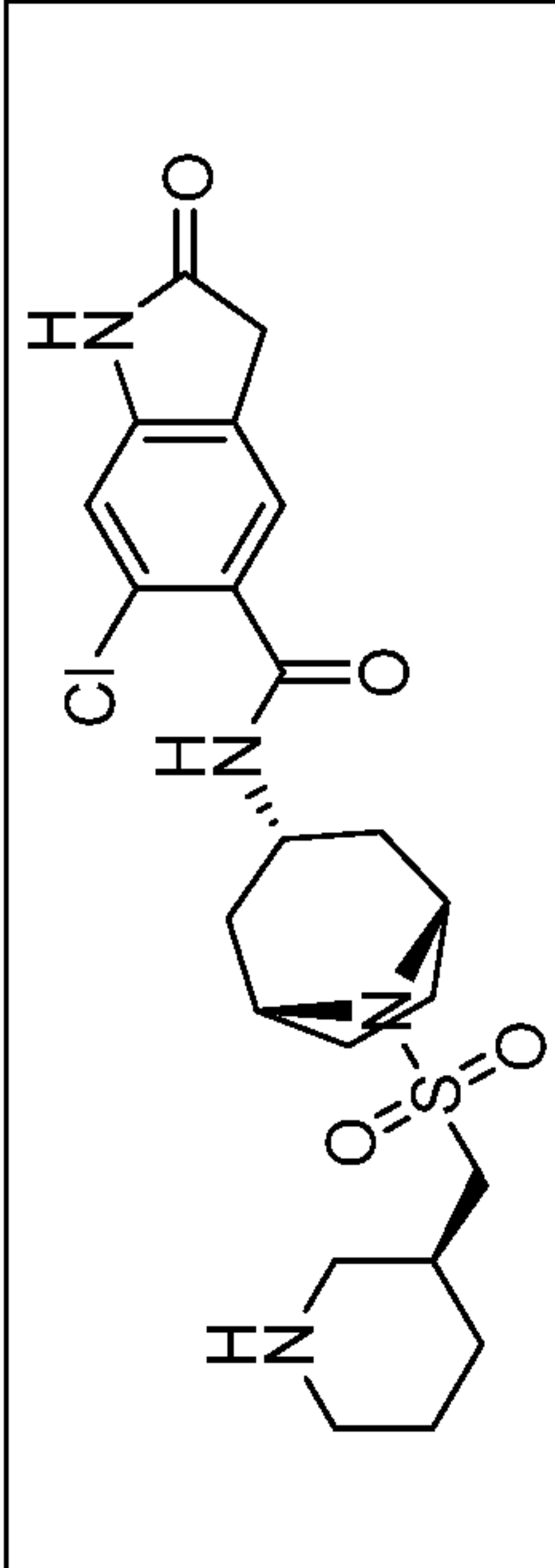
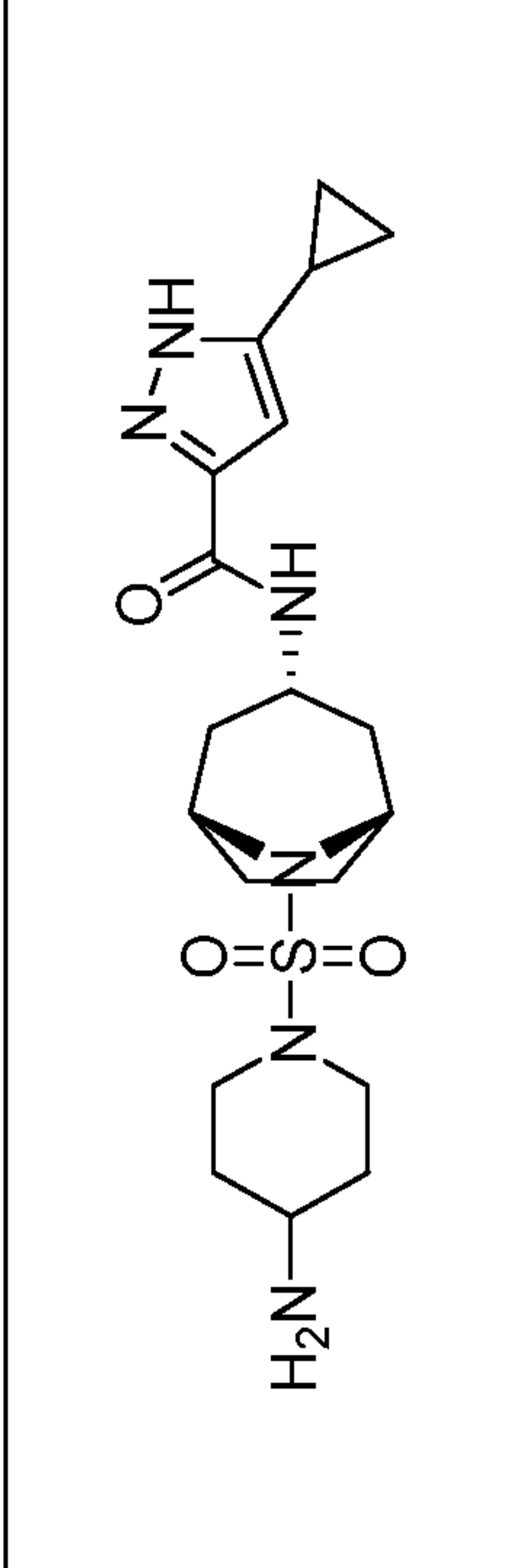
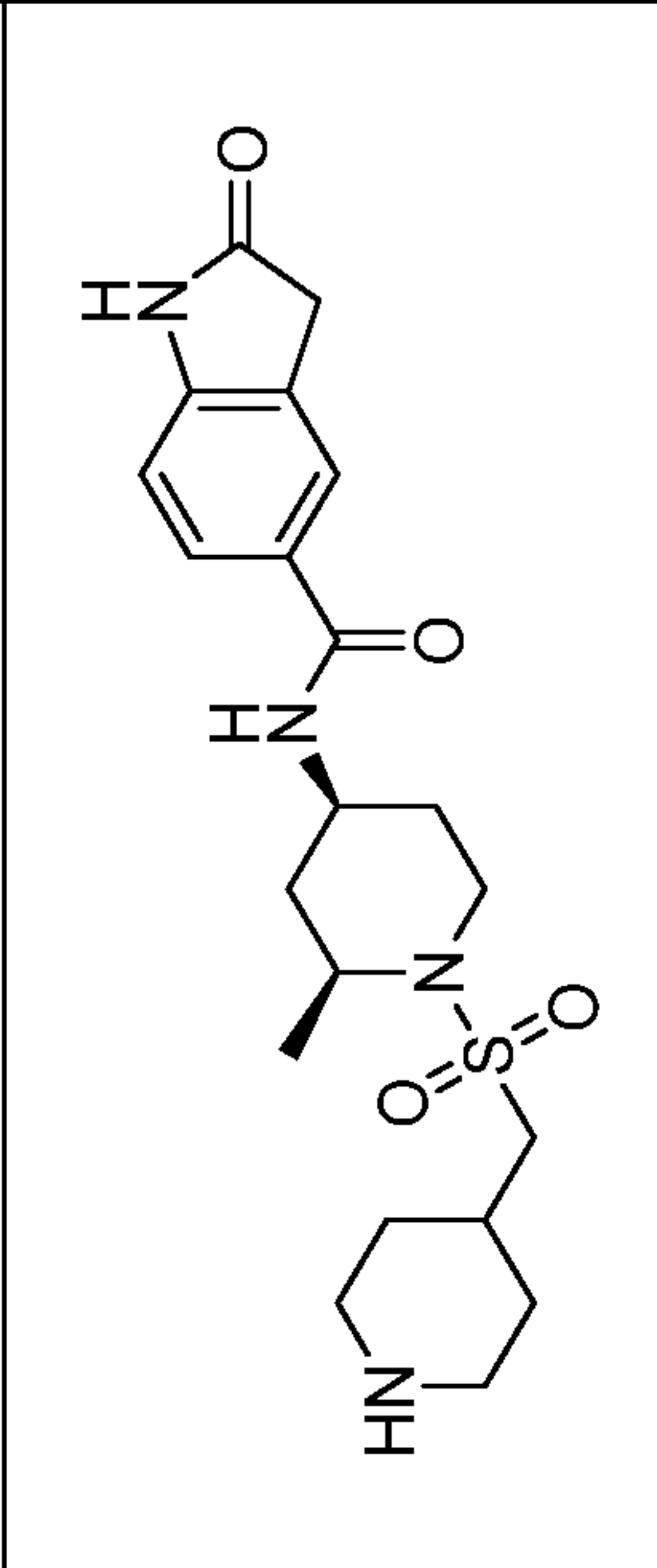
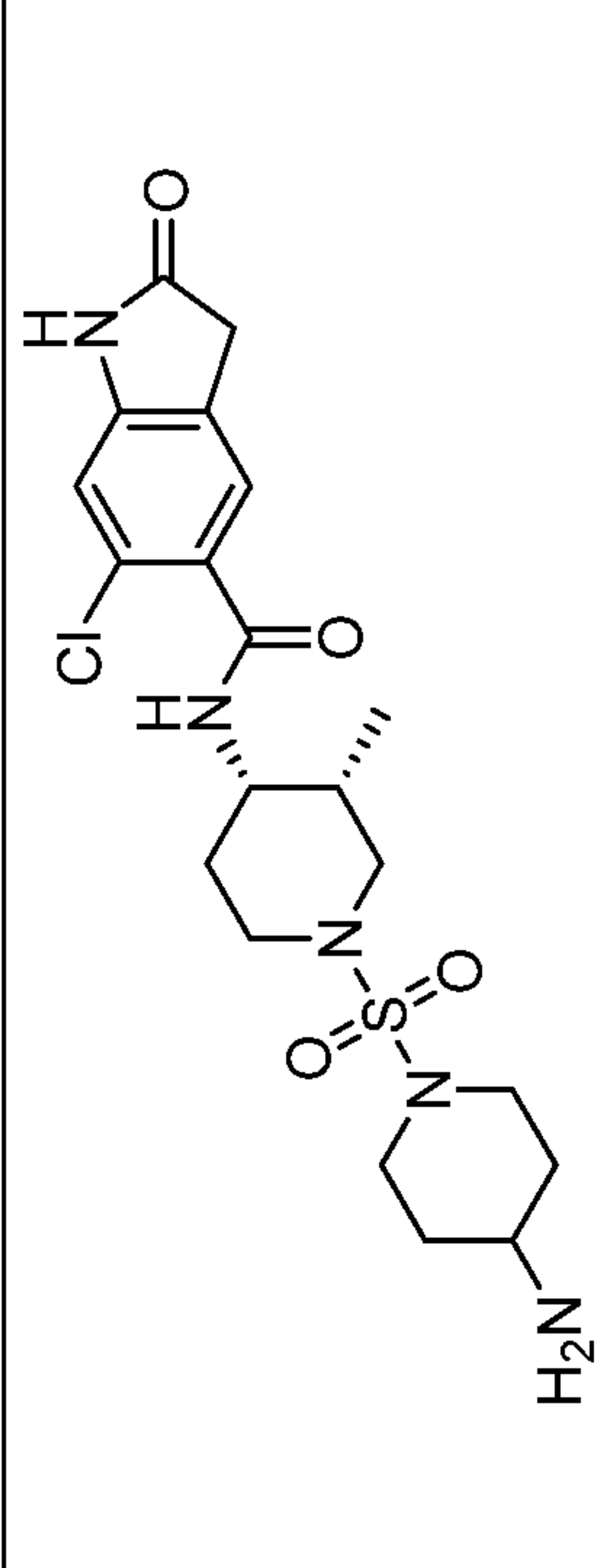
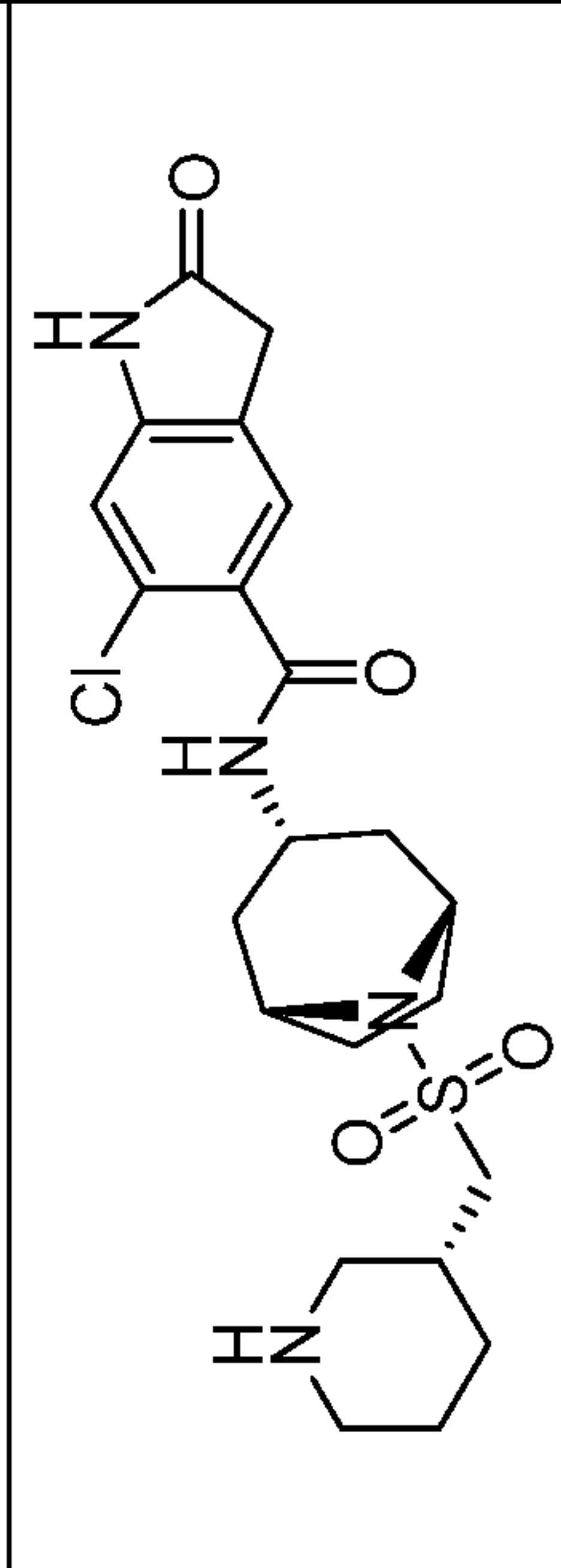
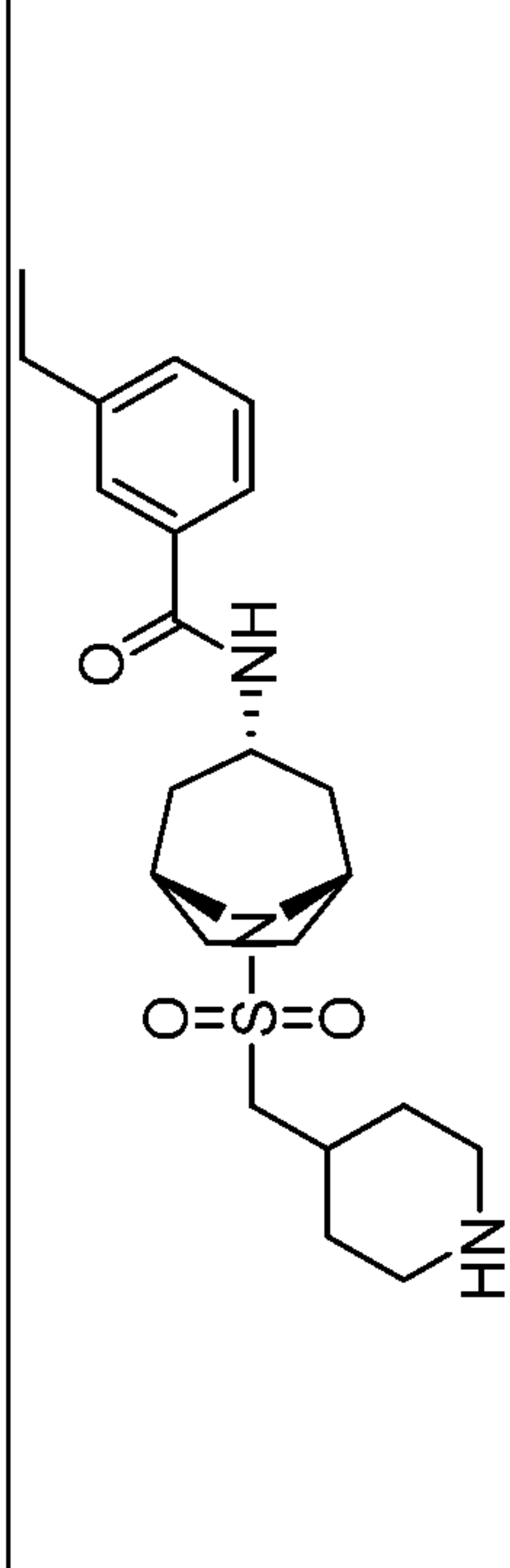
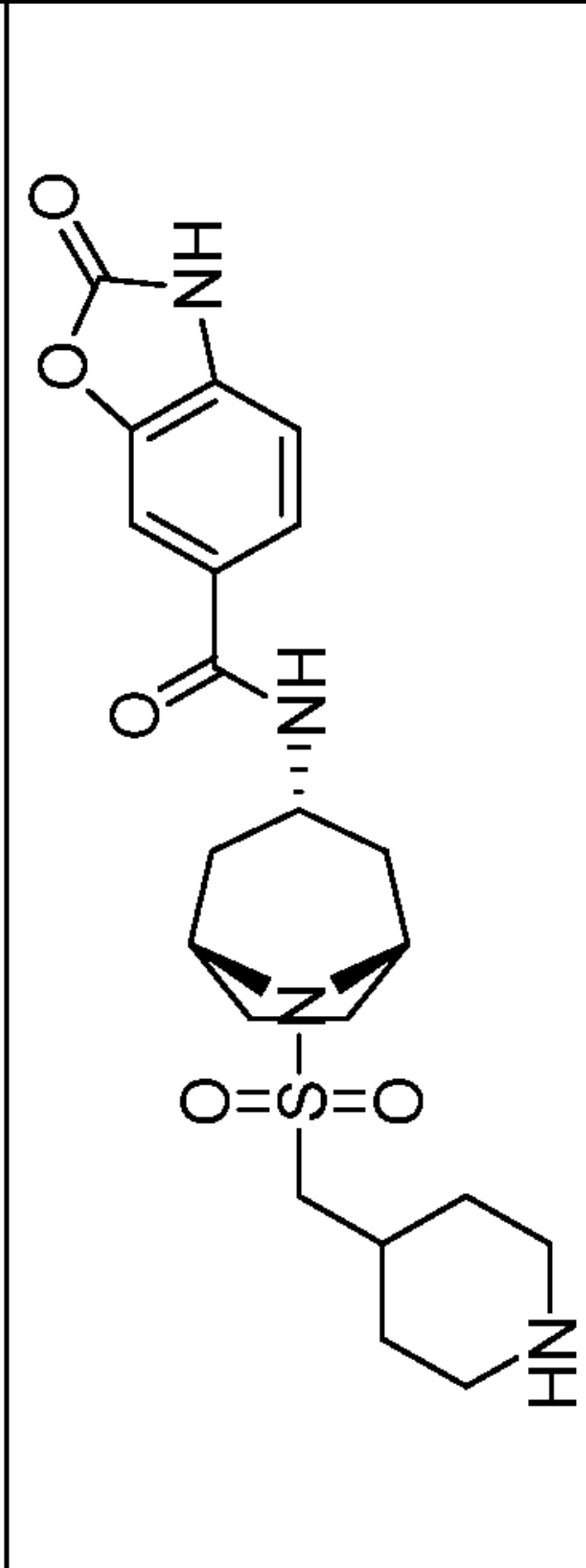
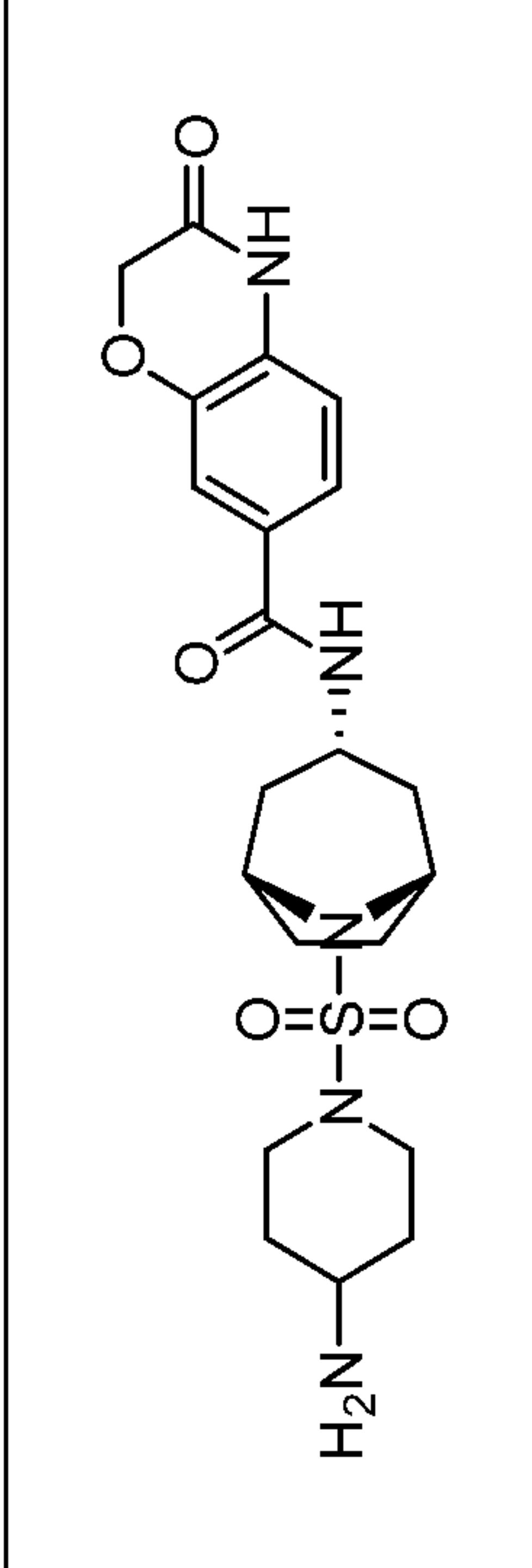
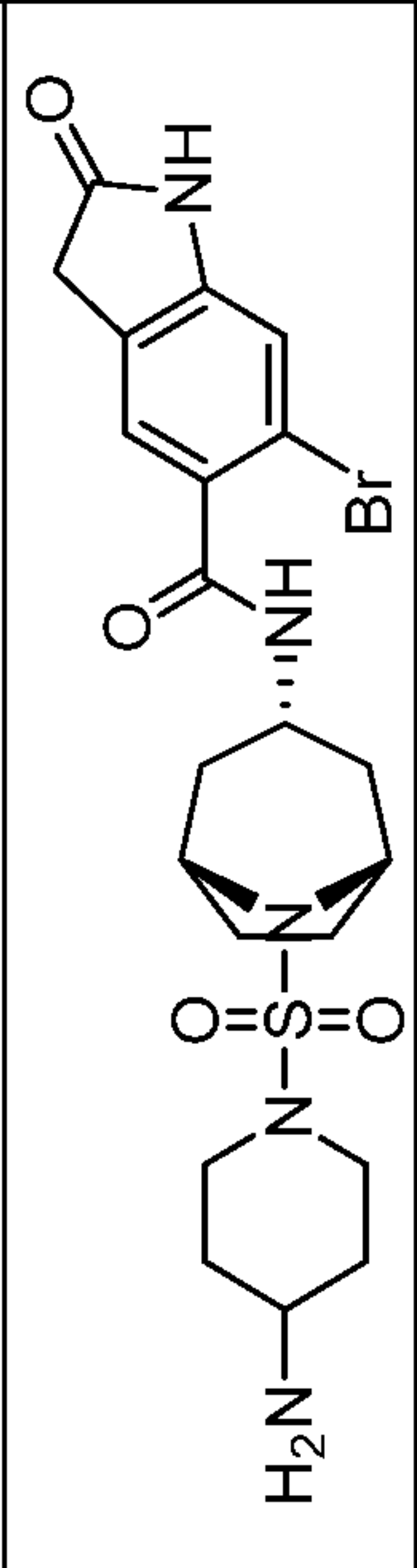
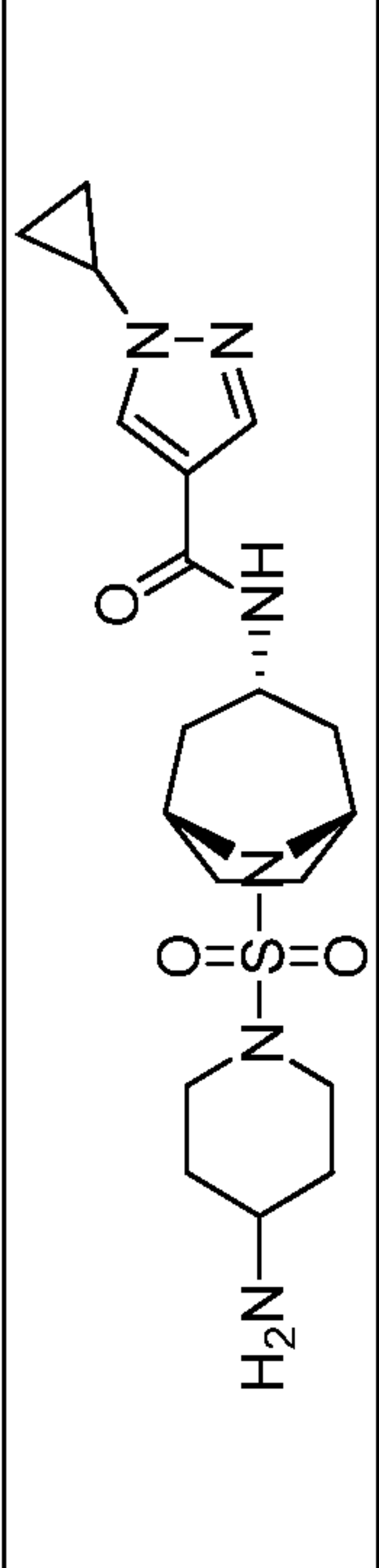
577		TFA	612		TFA
578		TFA	613		TFA
579		HCl	614		None
580		None	615		None
581		None	616		TFA

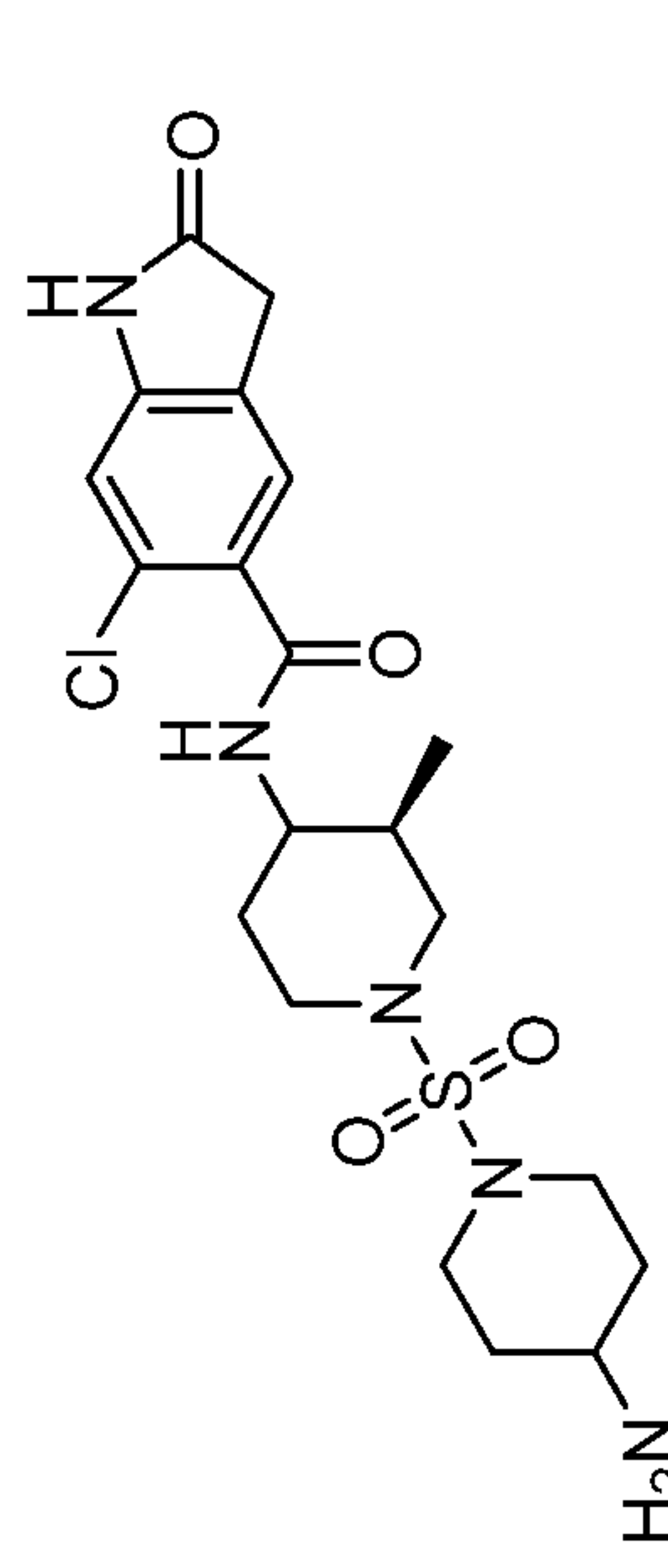
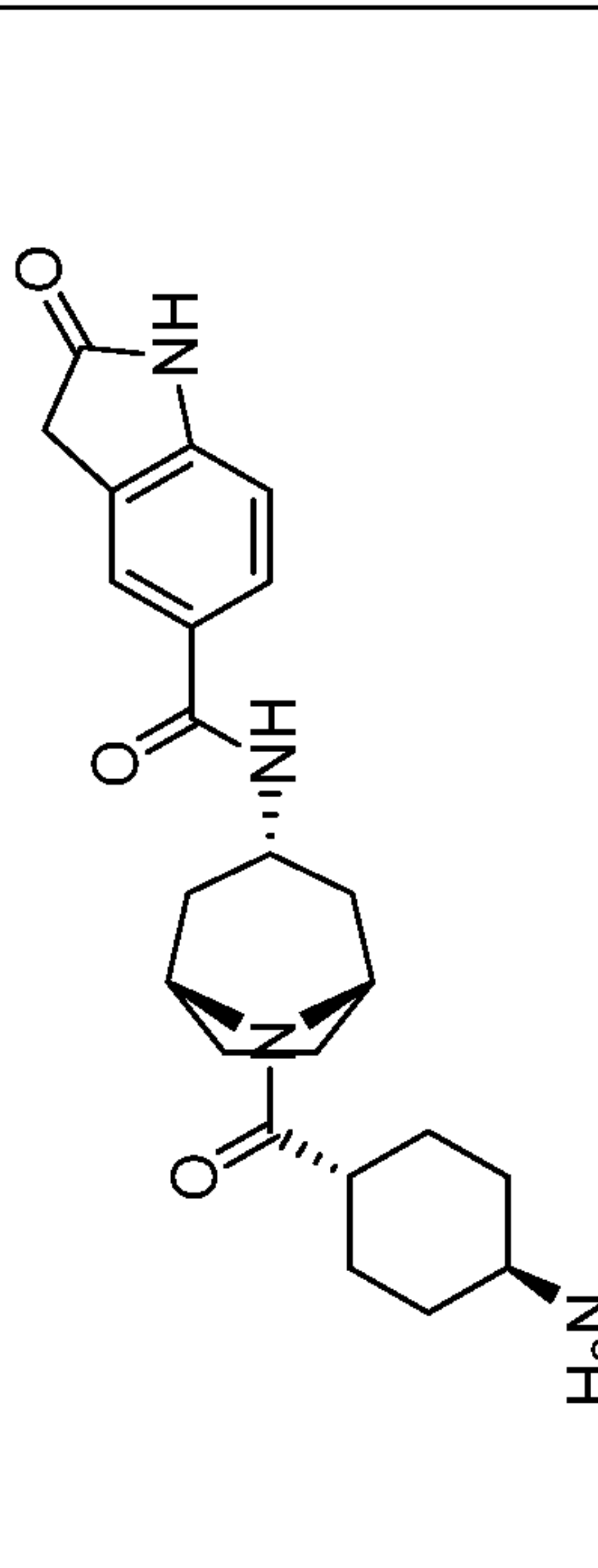
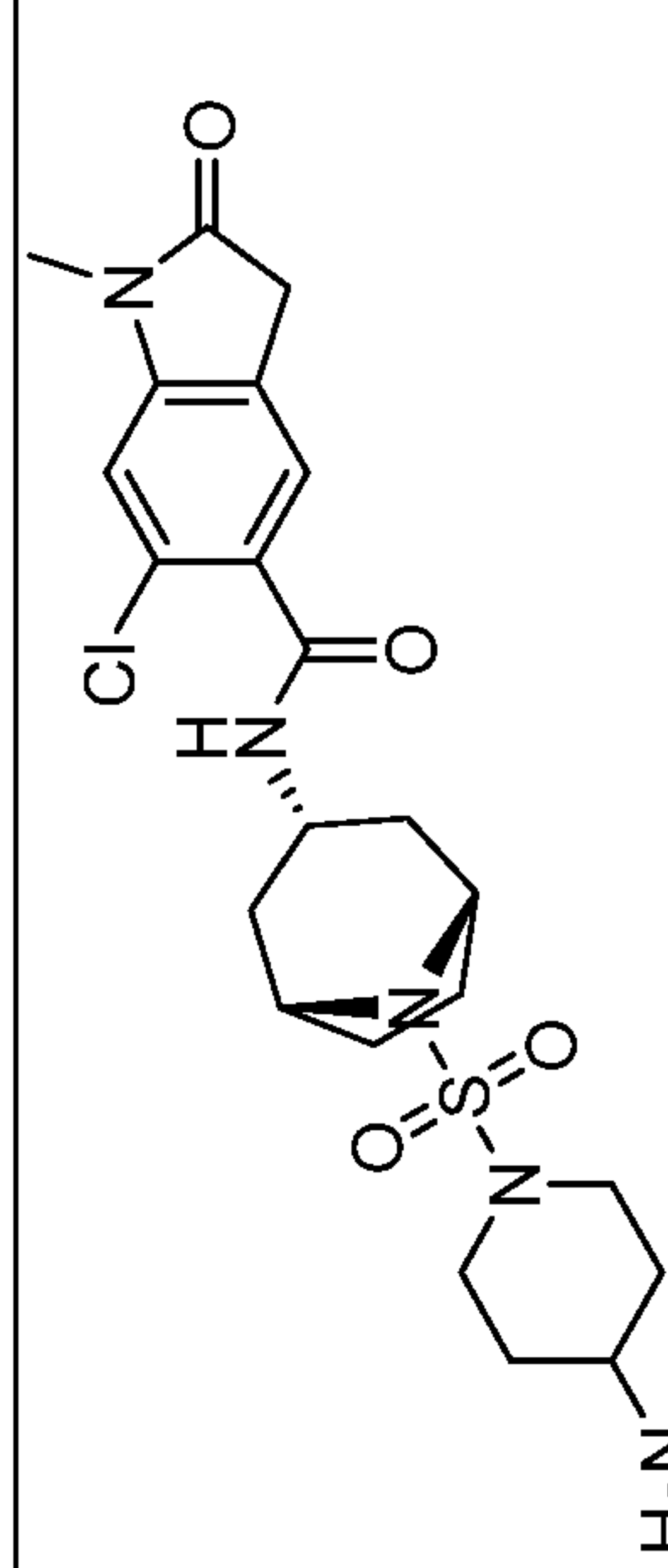
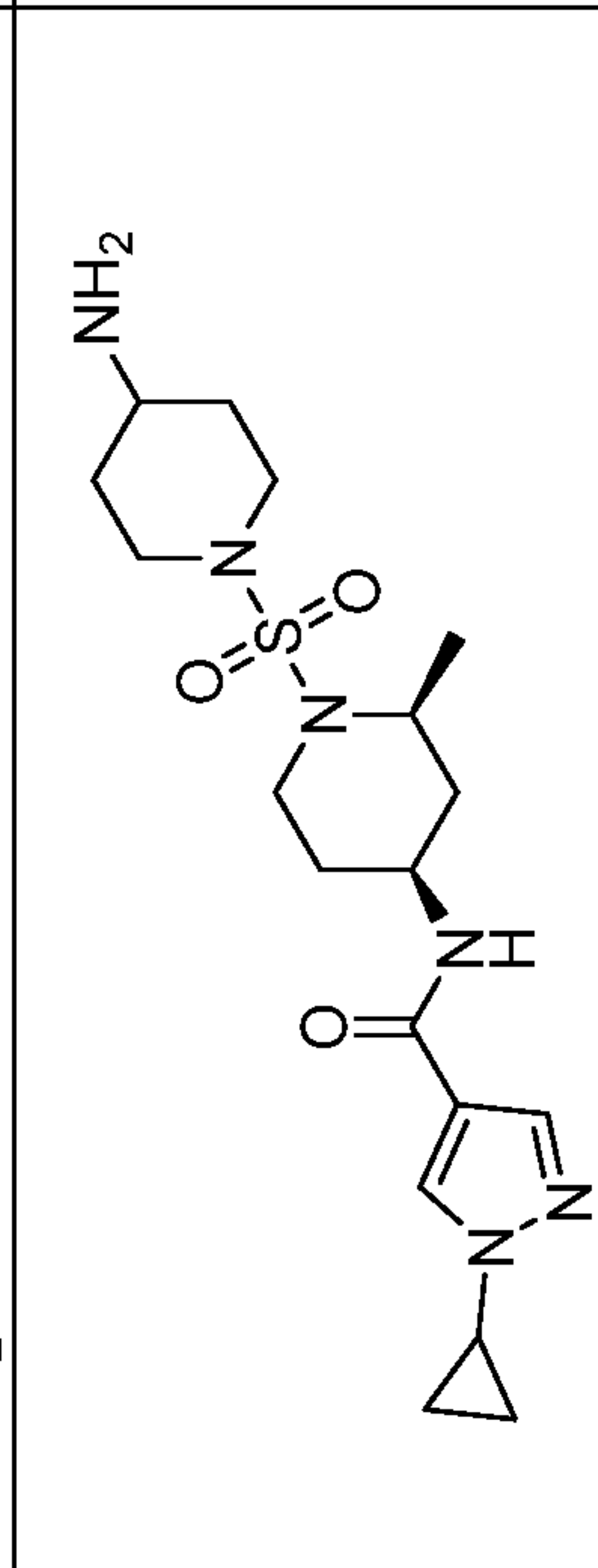
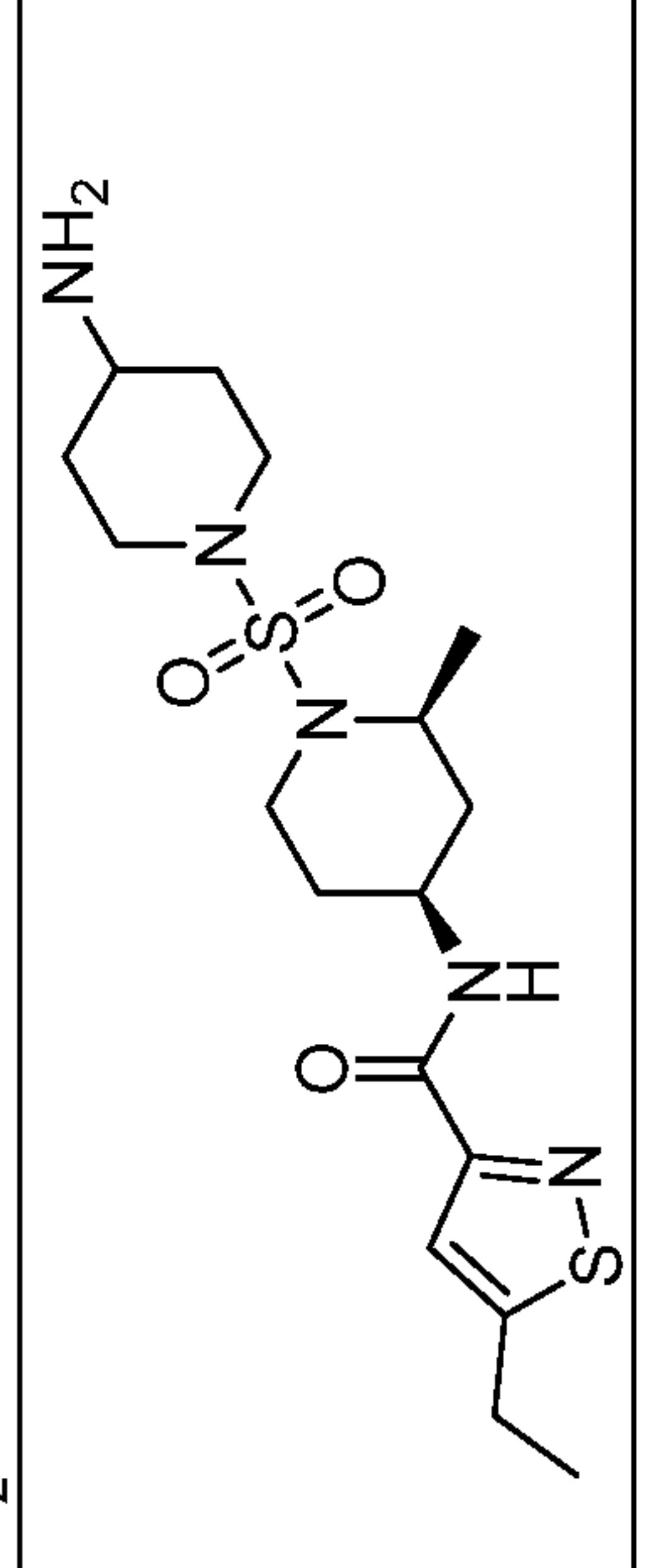
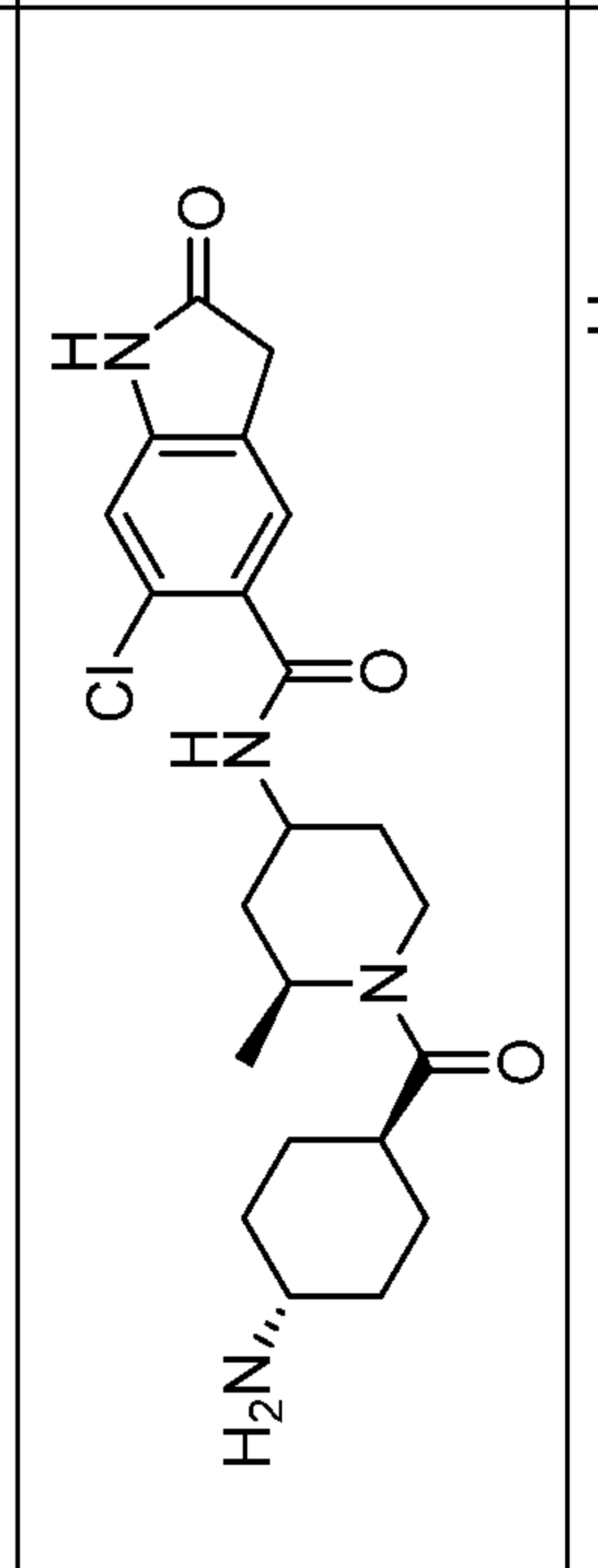
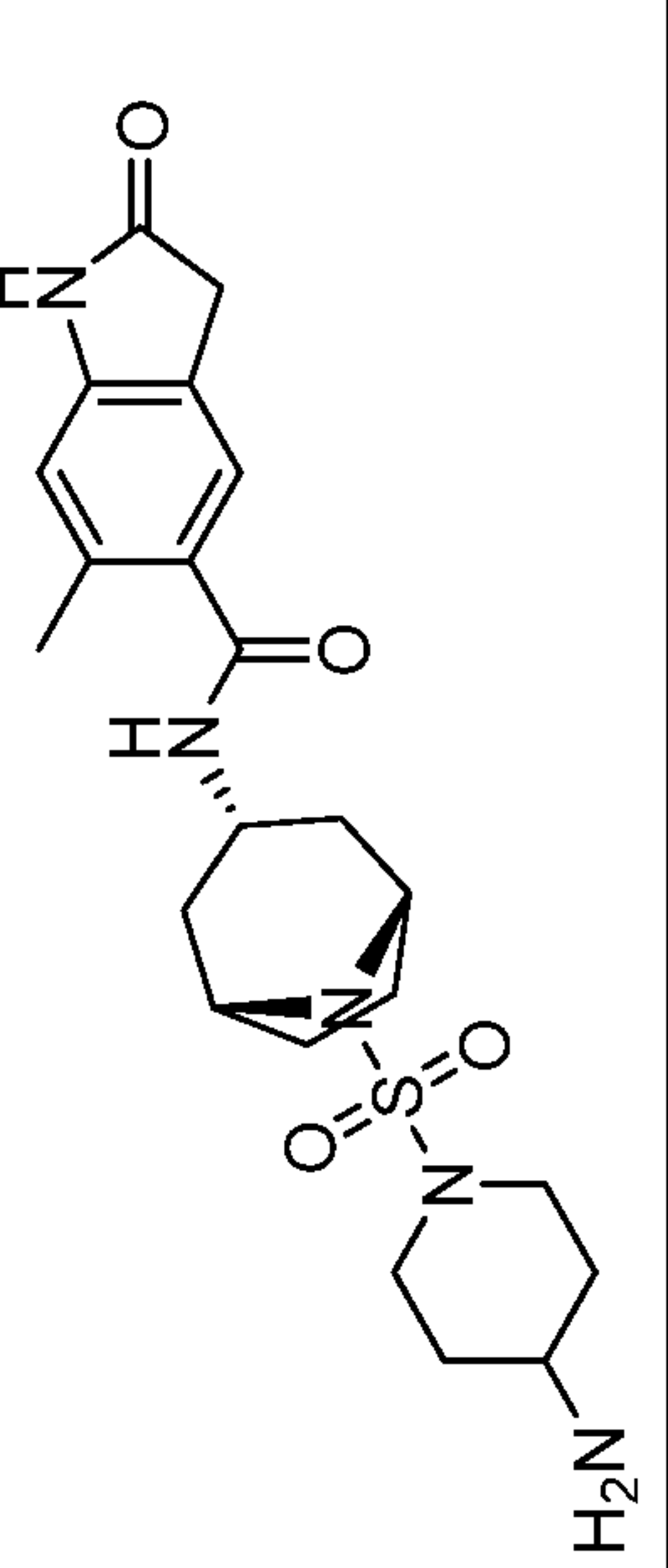
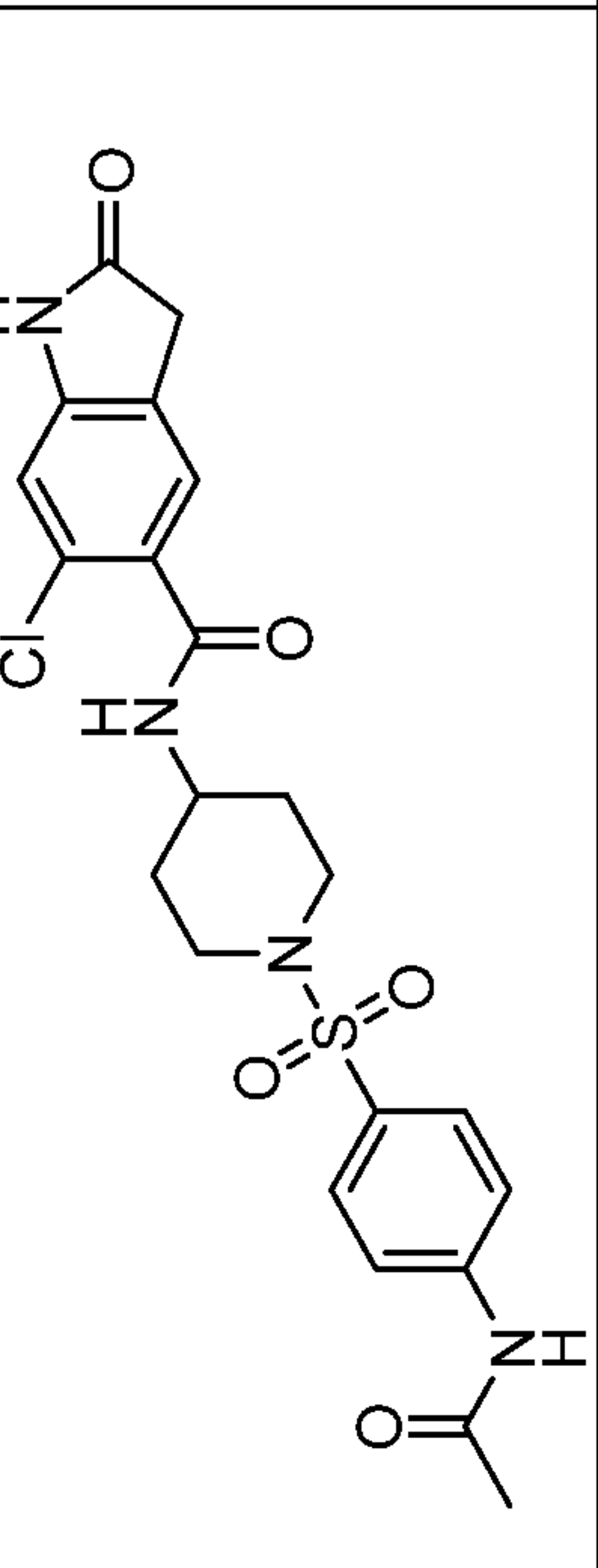
582		HCl	617		TFA
583		TFA	618		HCl
584		TFA	619		TFA
585		TFA	620		TFA

586		HCl	621		TFA
587		TFA	622		TFA
588		TFA	623		None
589		HCl	624		None

590		None	625		HCl
591		TFA	626		HCl
592		TFA	627		HCl
593		None	628		HCl

594		None	629		None
595		None	630		None
596		TFA	631		HCl
597		HCl	632		None

598		TFA	633		None
599		TFA	634		None
600		TFA	635		HCl
601		HCl	636		HCl
602		None	637		None

603		TFA	638		TFA
604		TFA	639		None
605		HCl	640		TFA
606		None	641		None

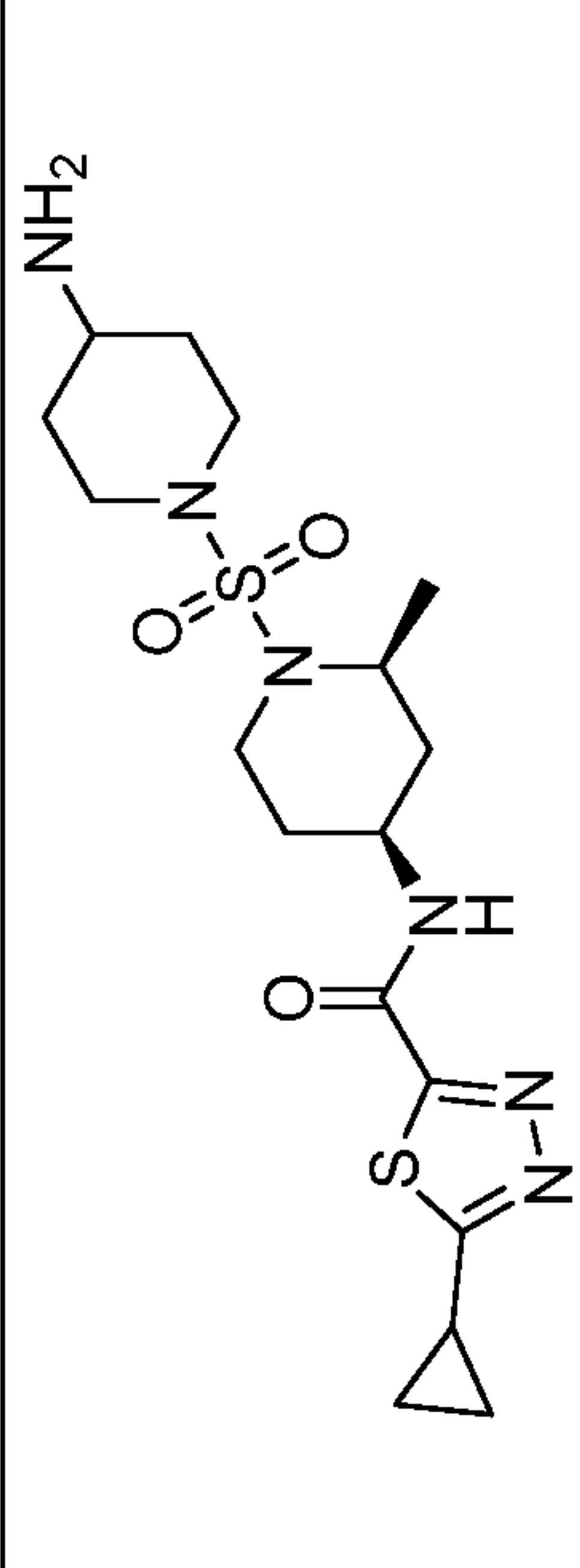
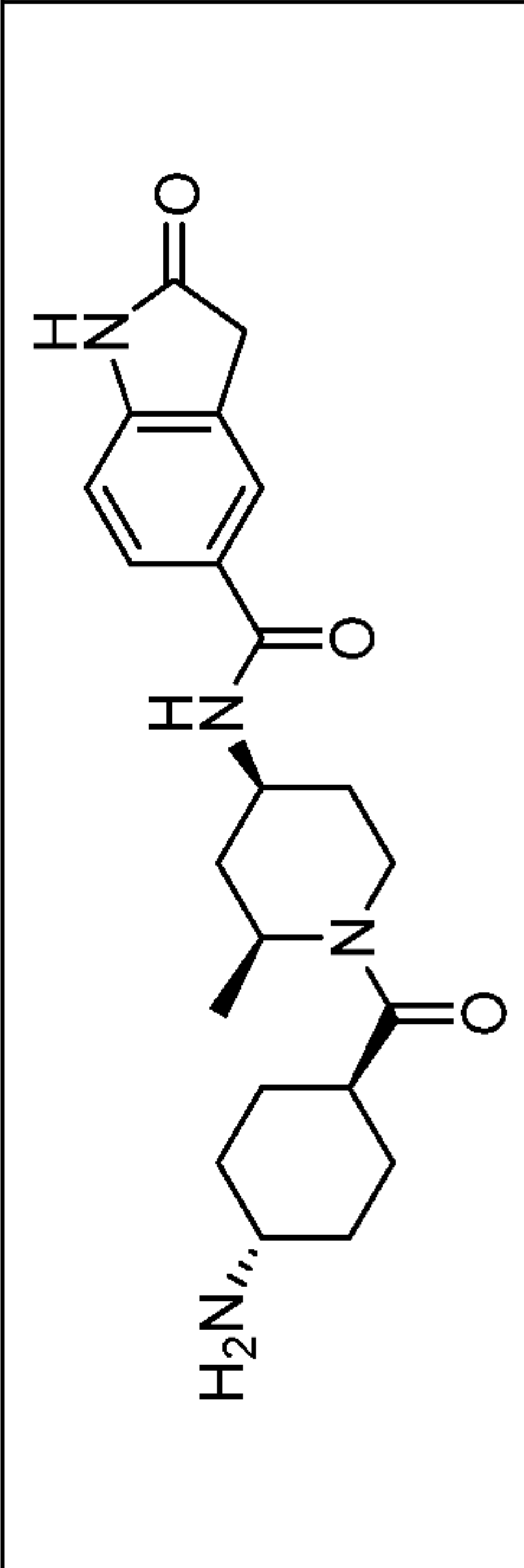
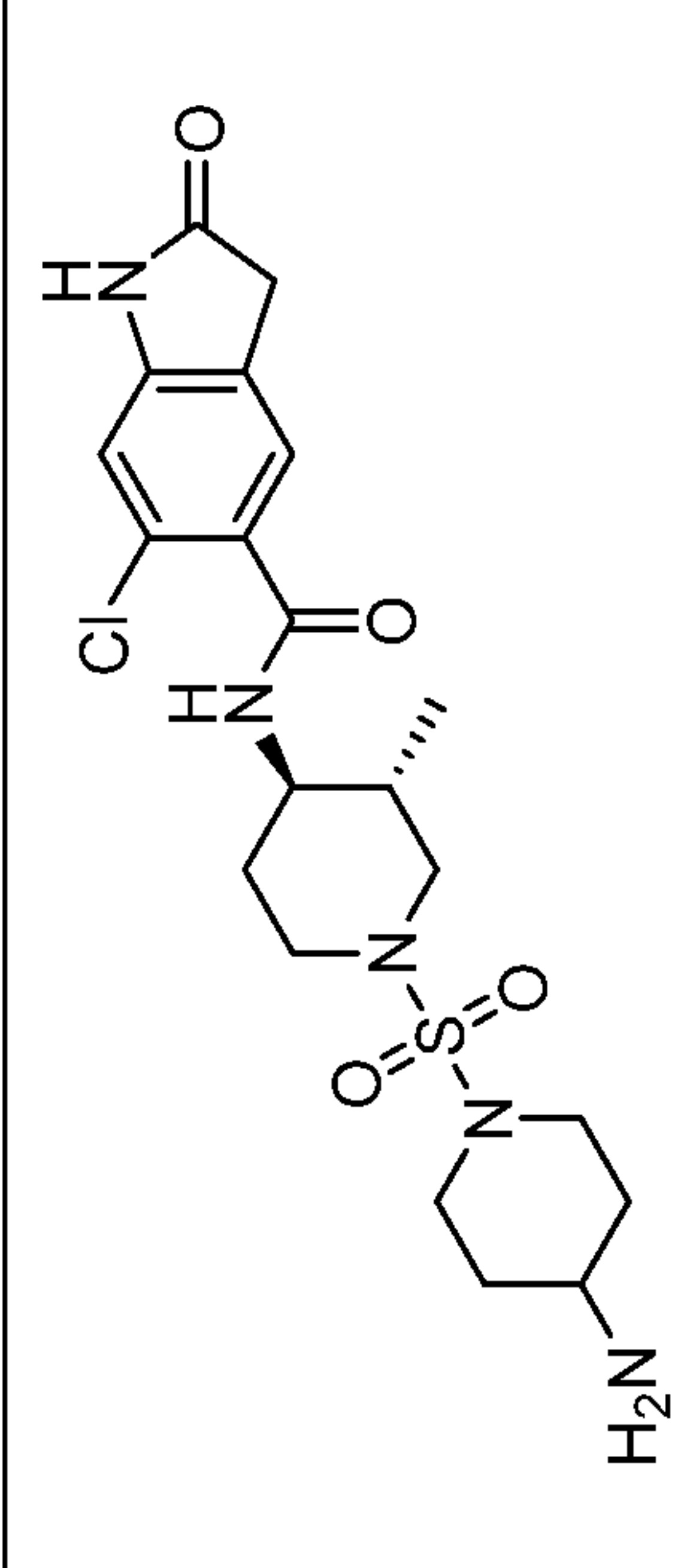
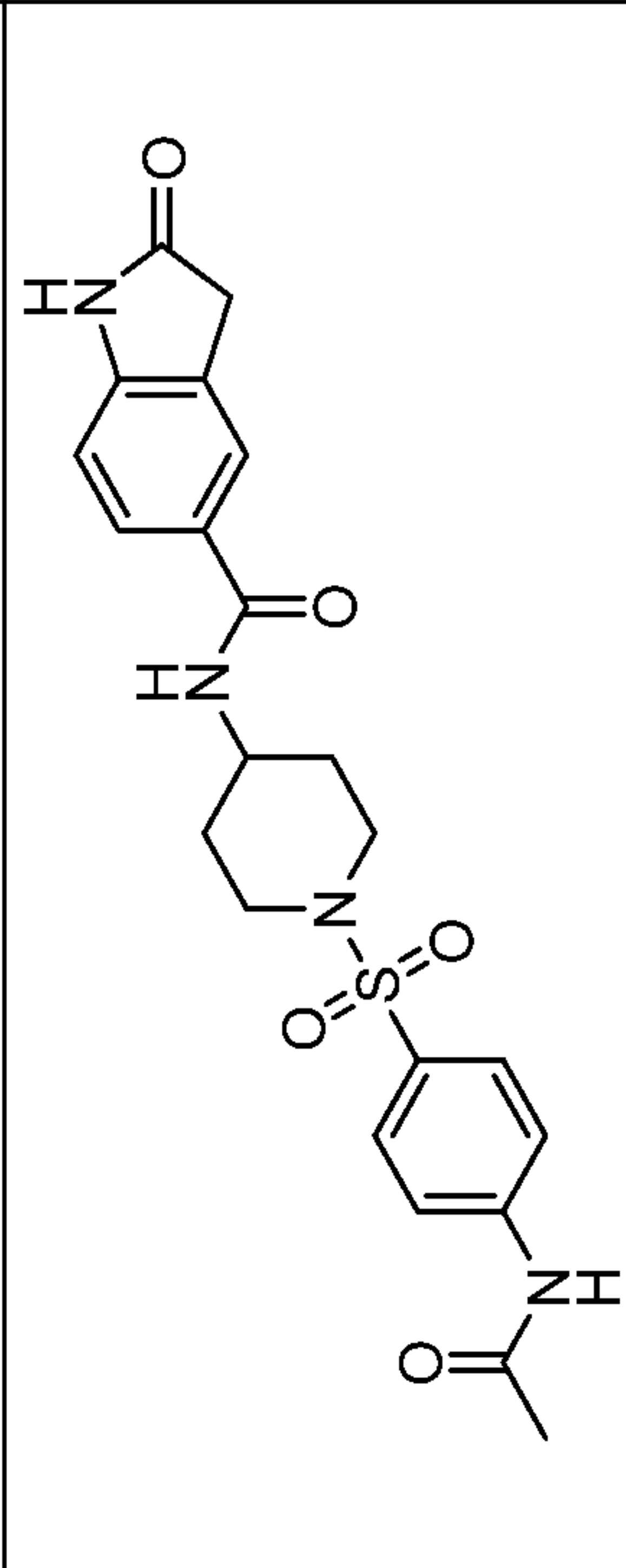
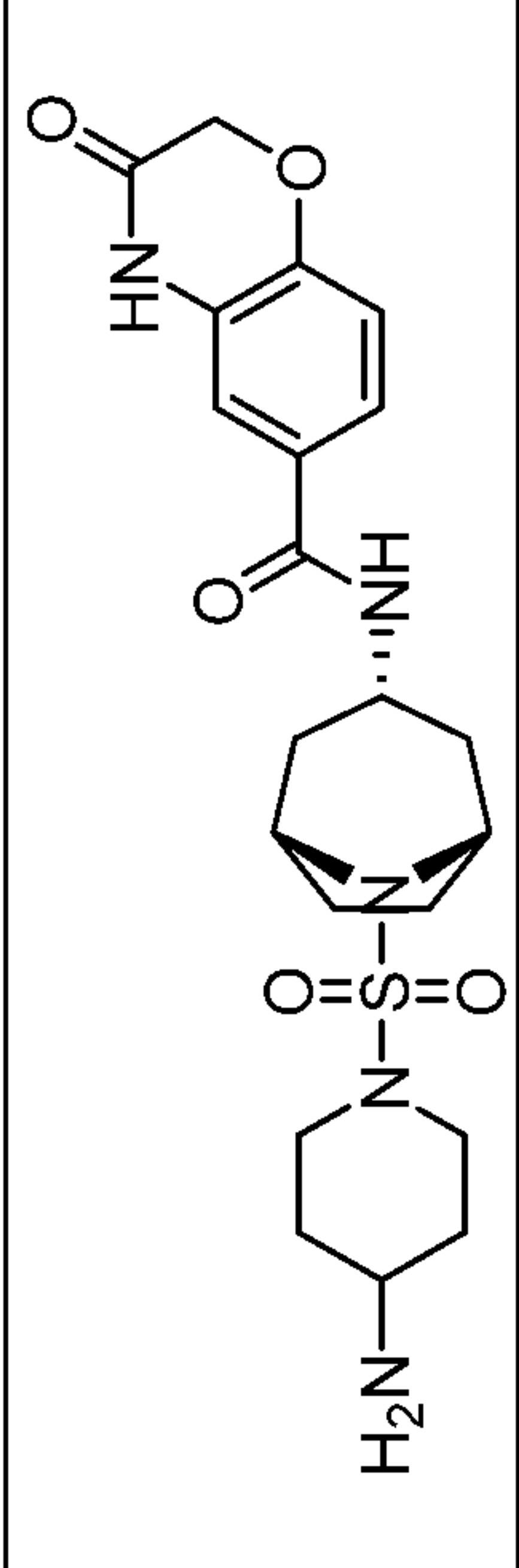
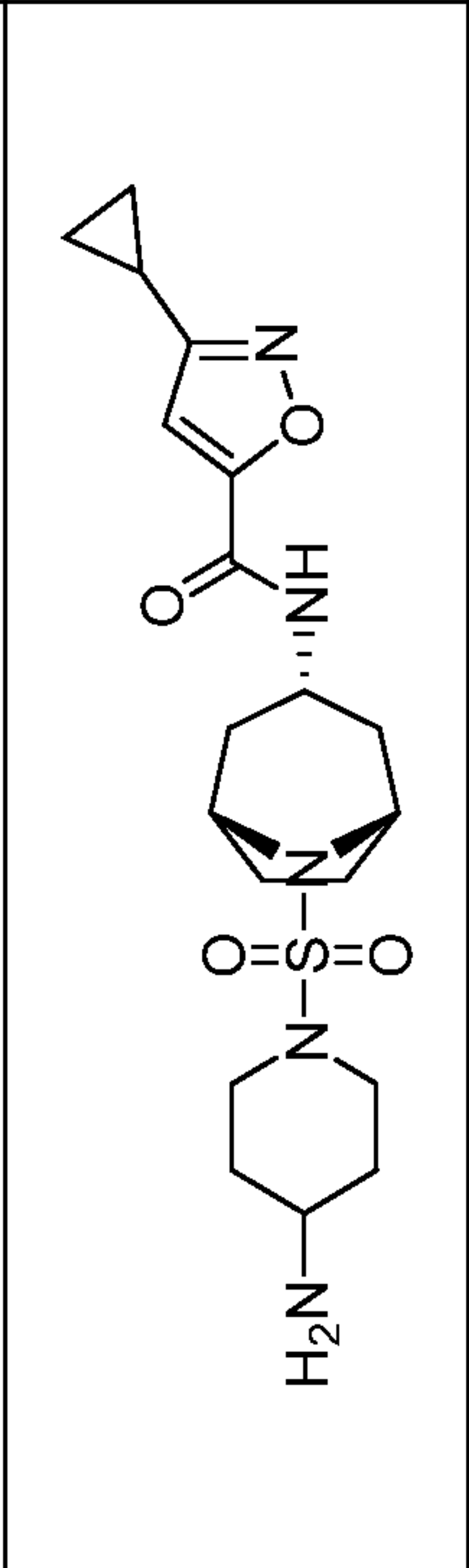
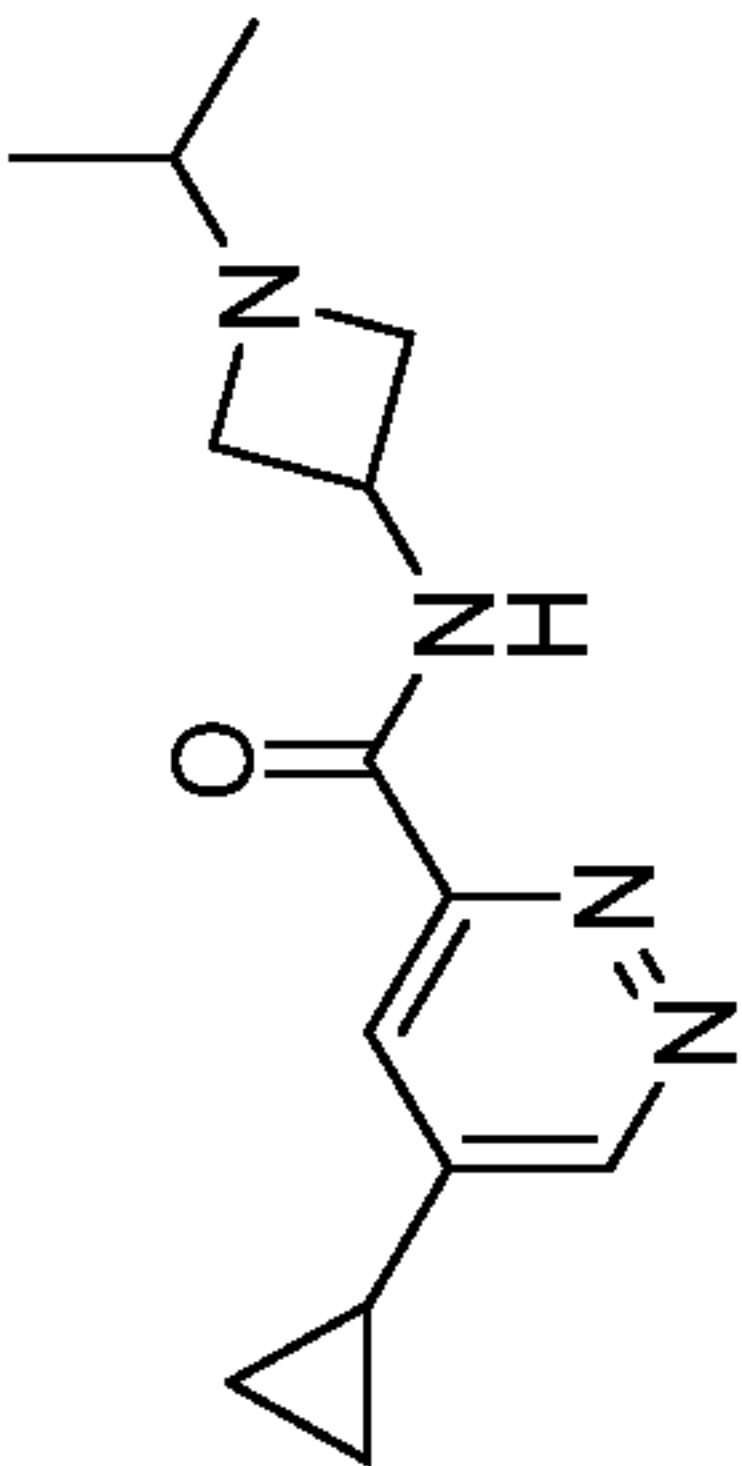
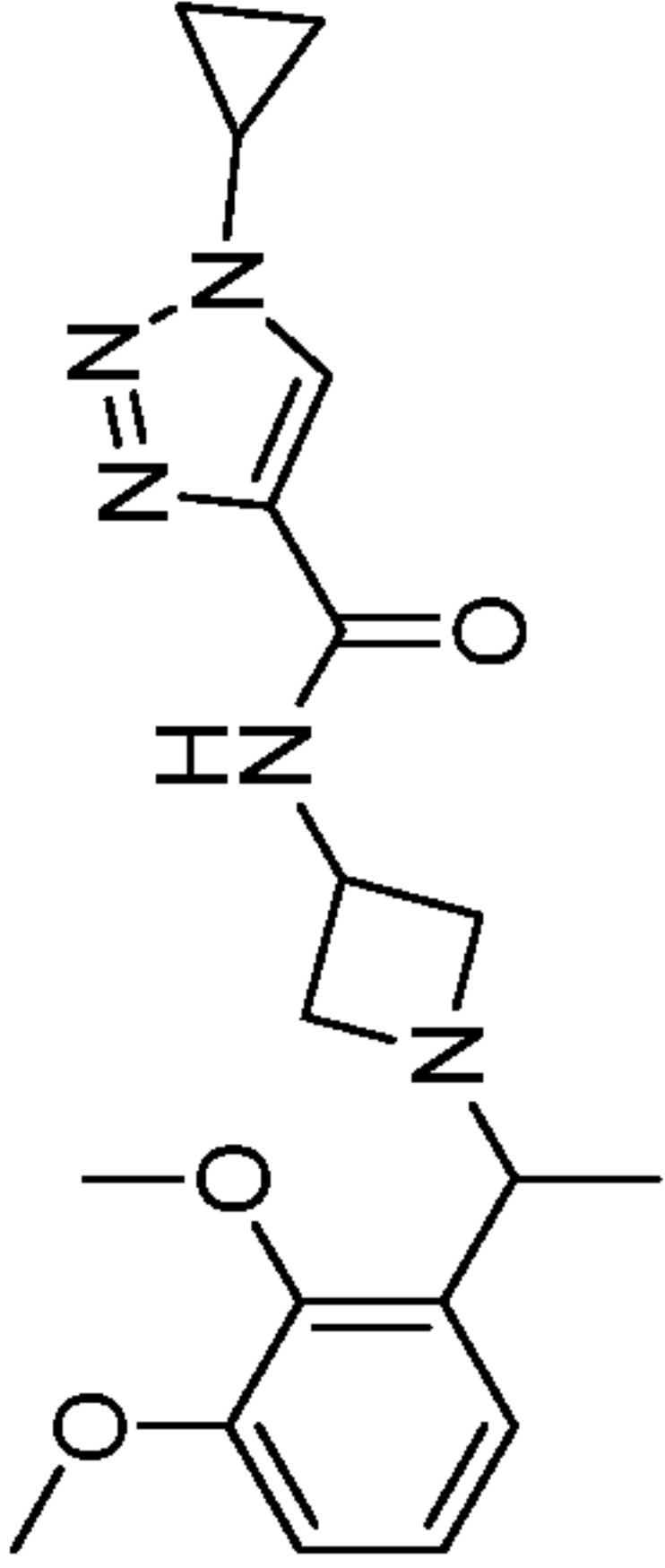
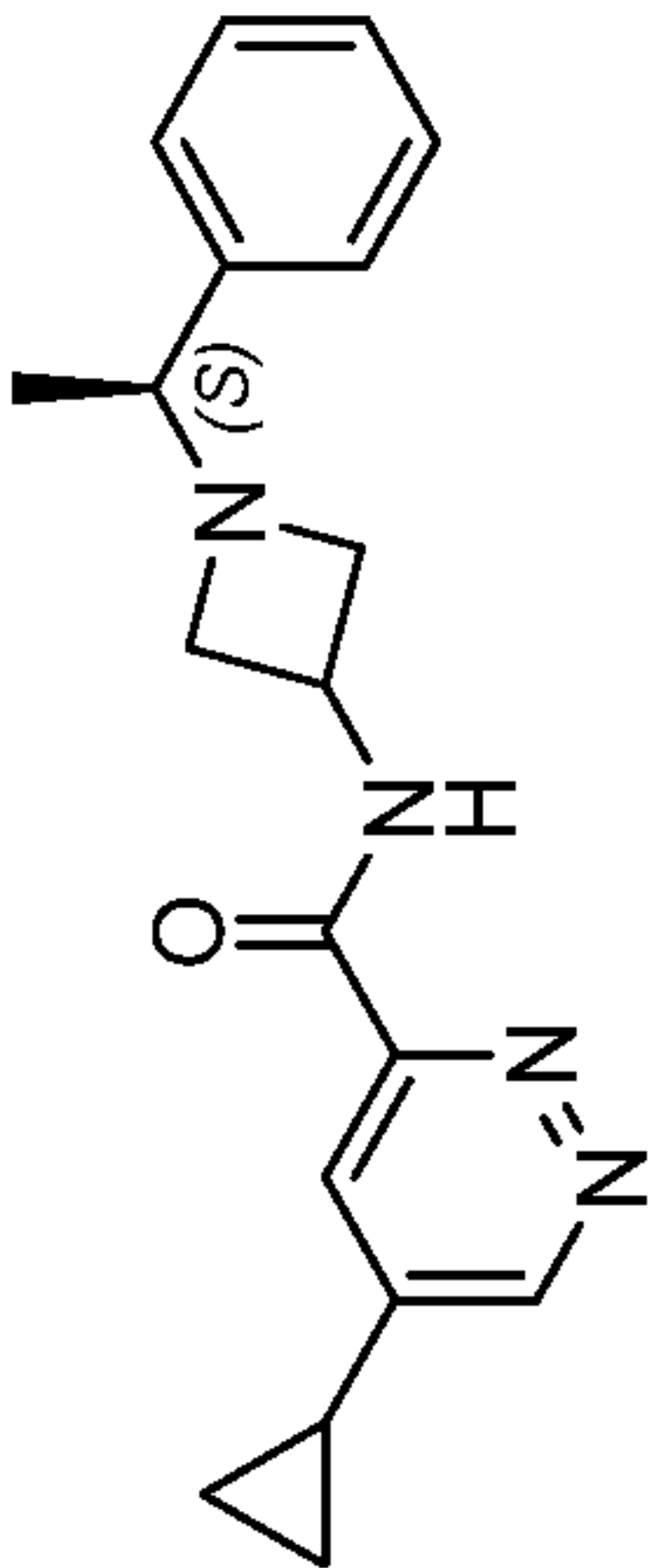
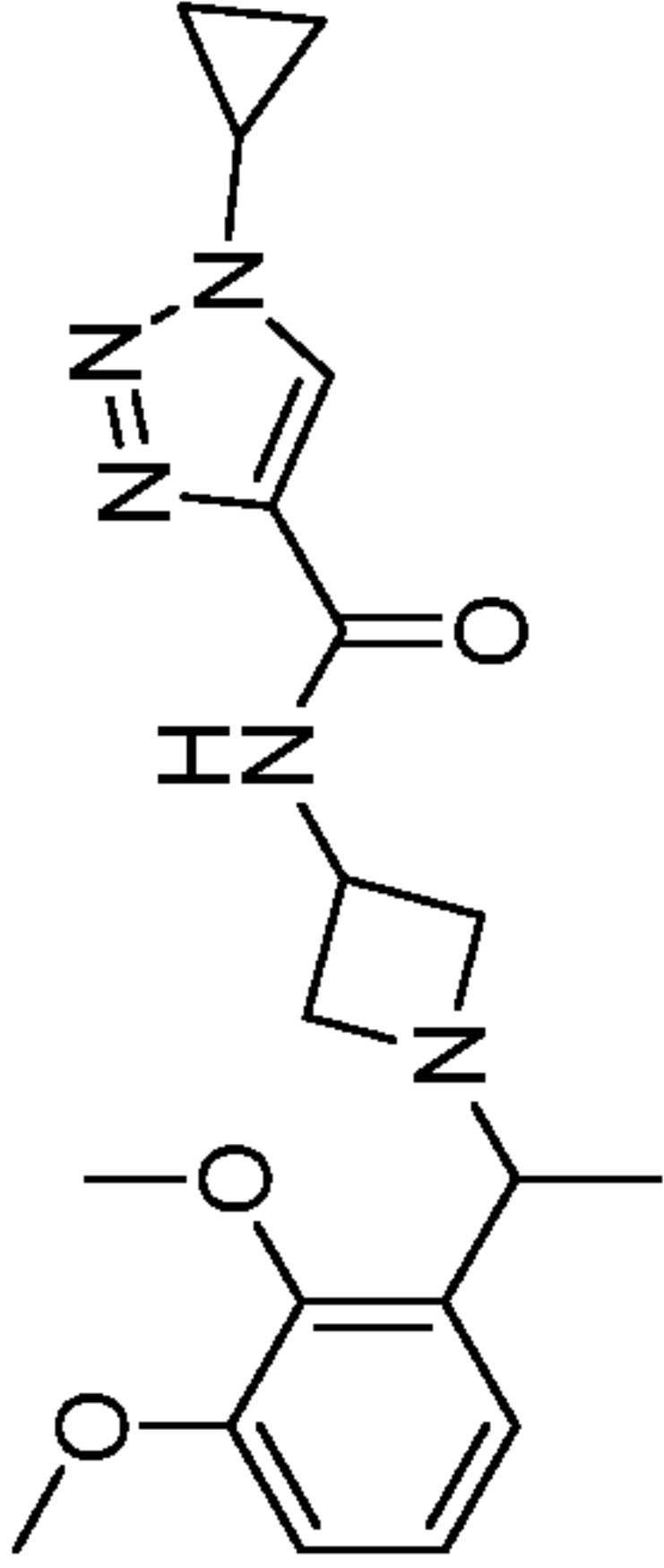
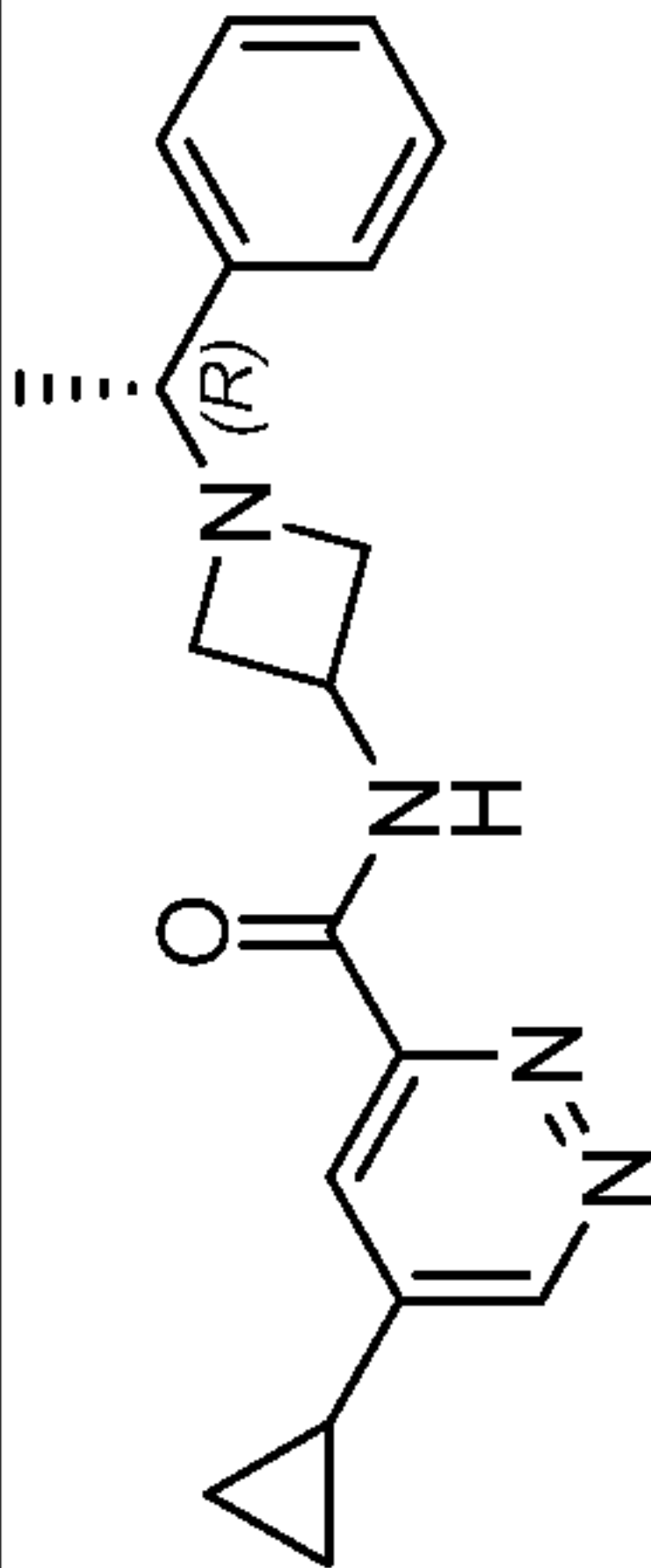
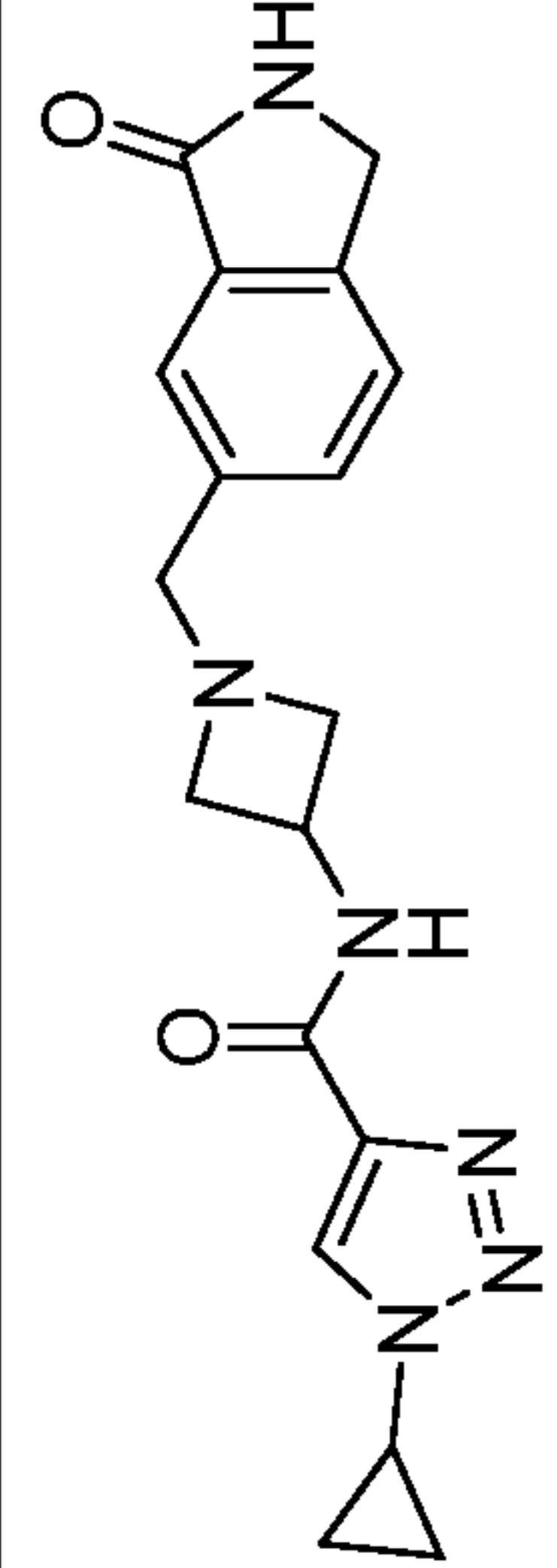
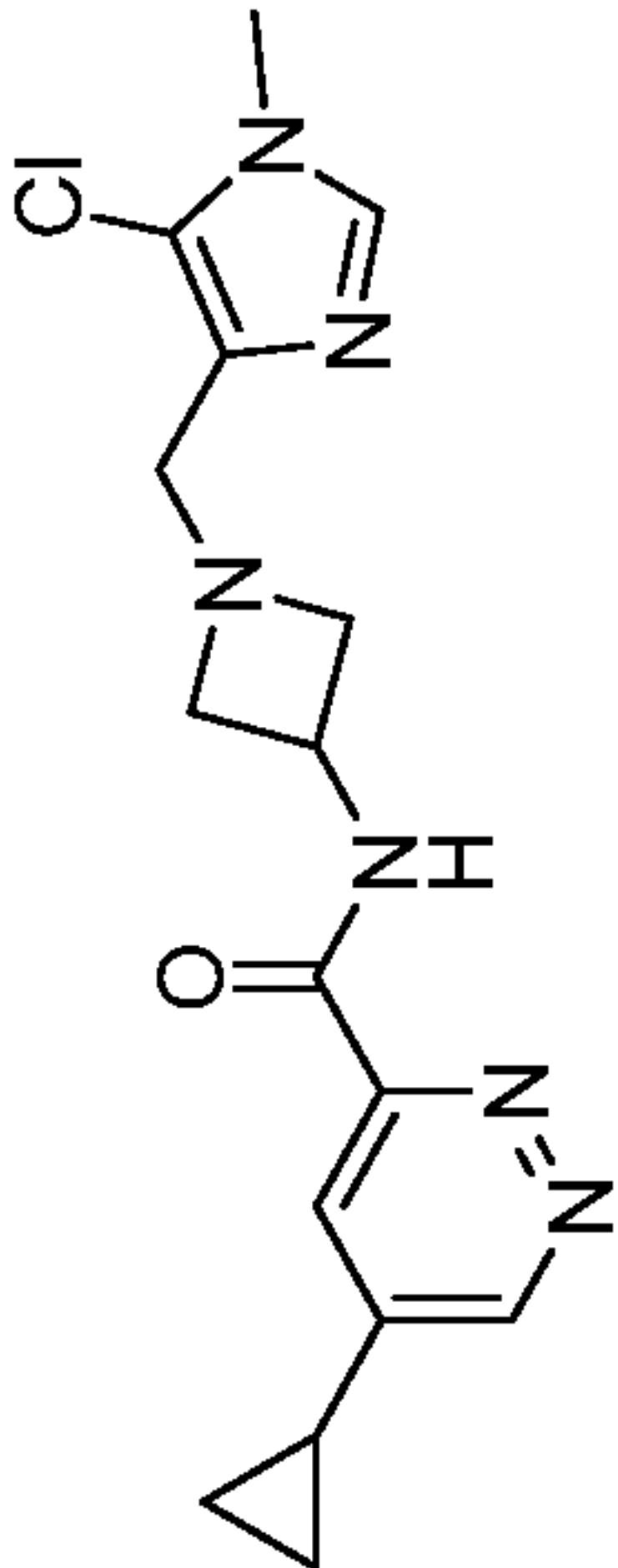
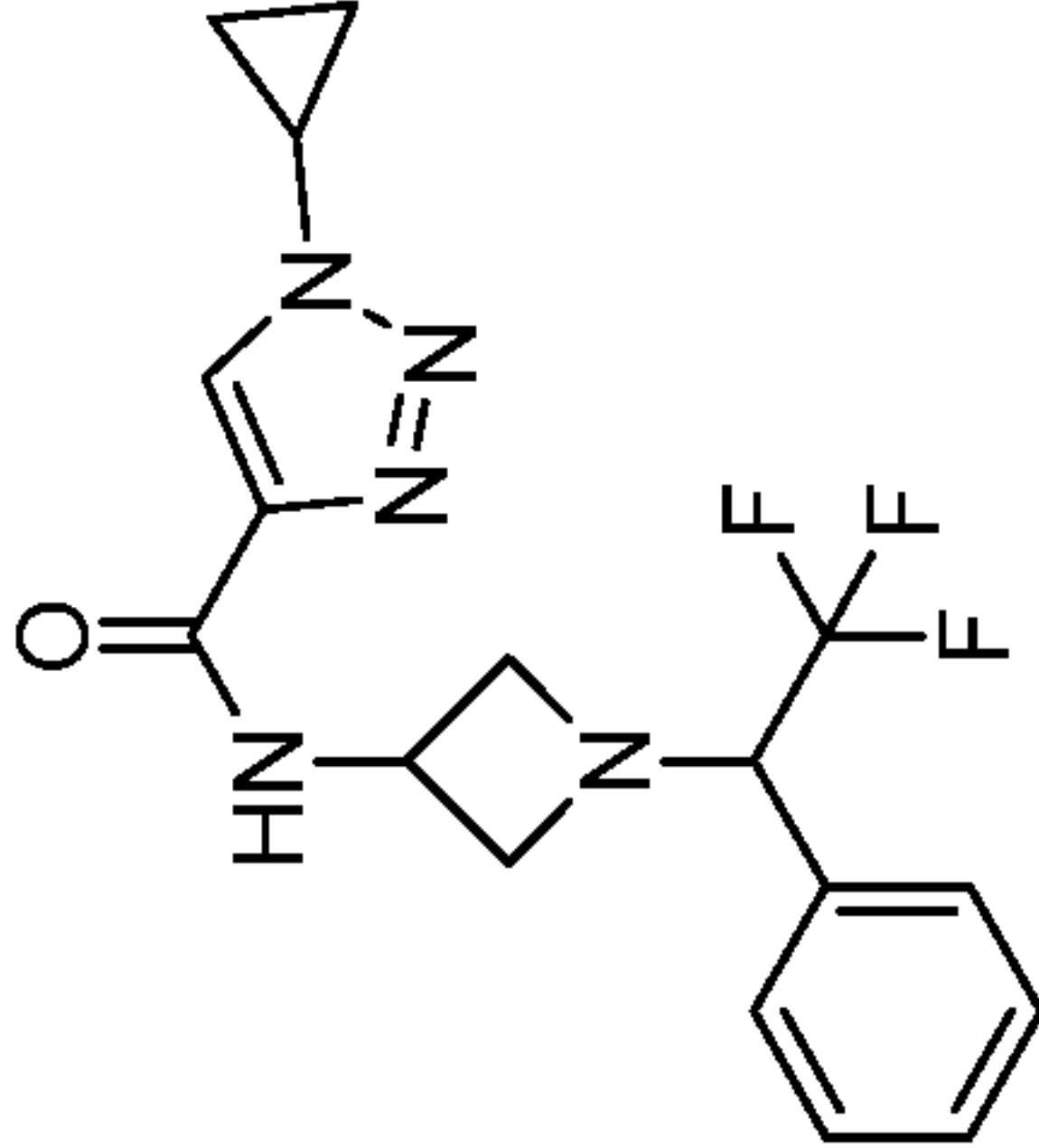
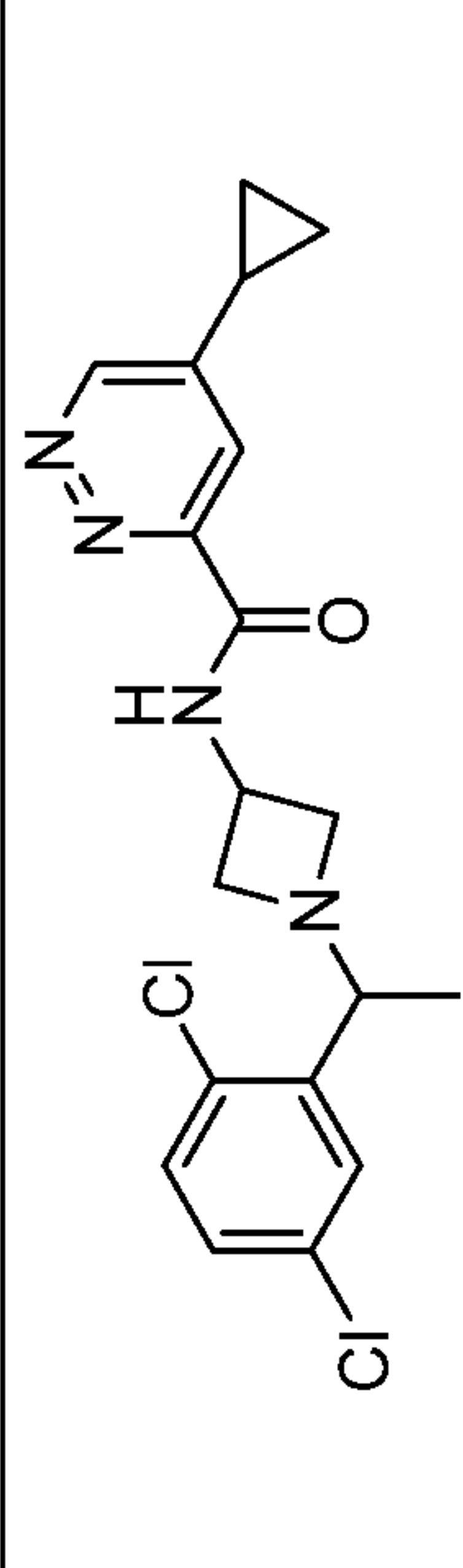
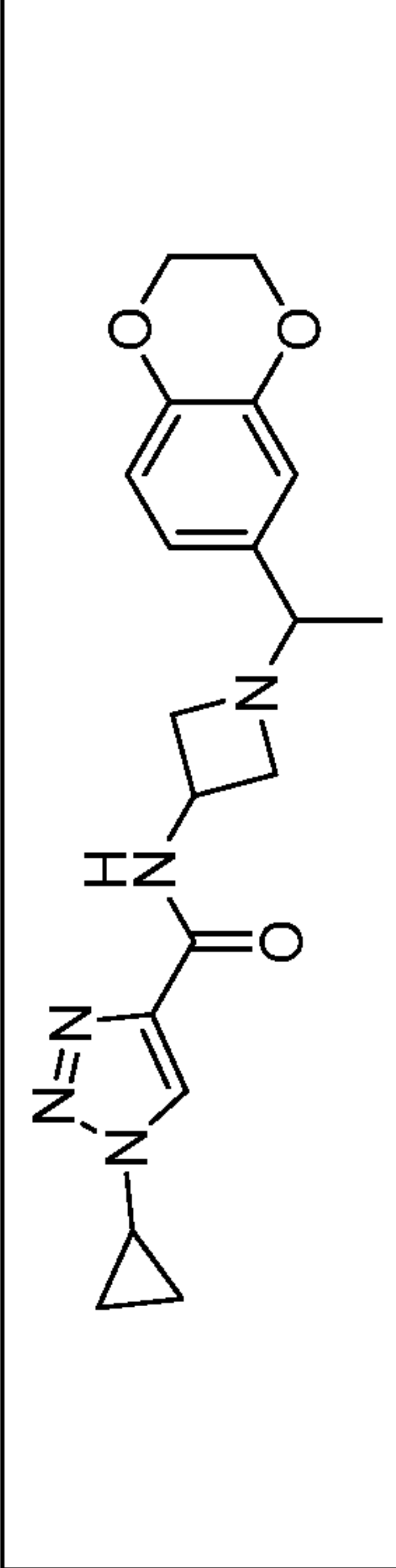
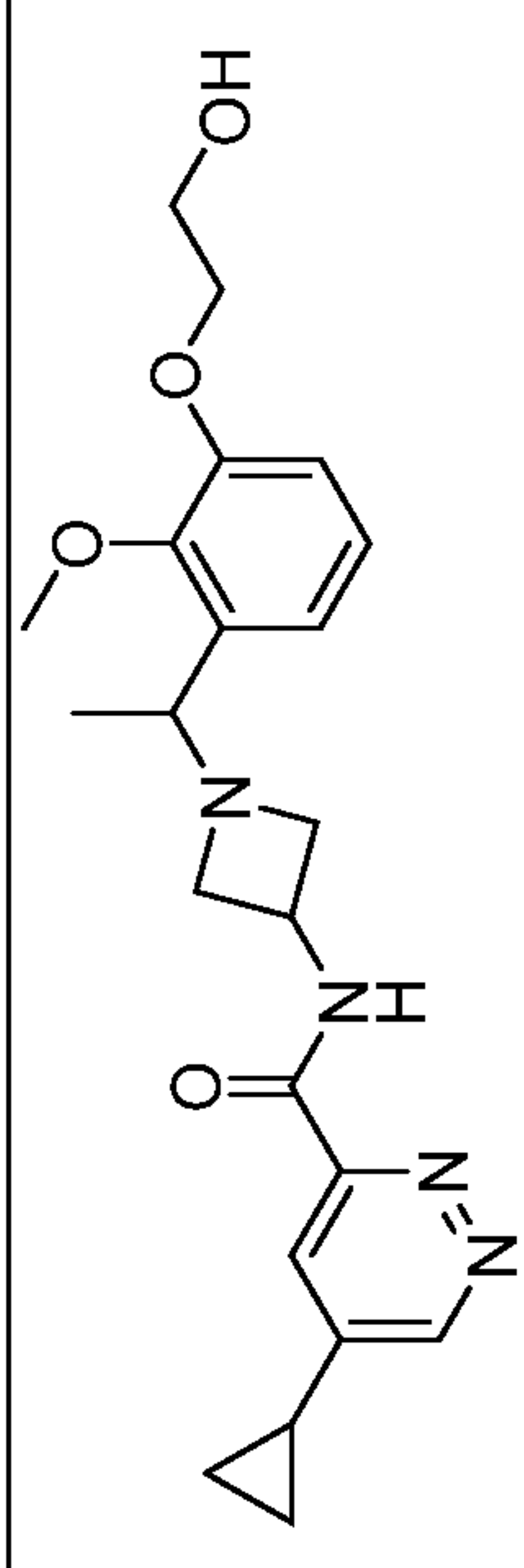
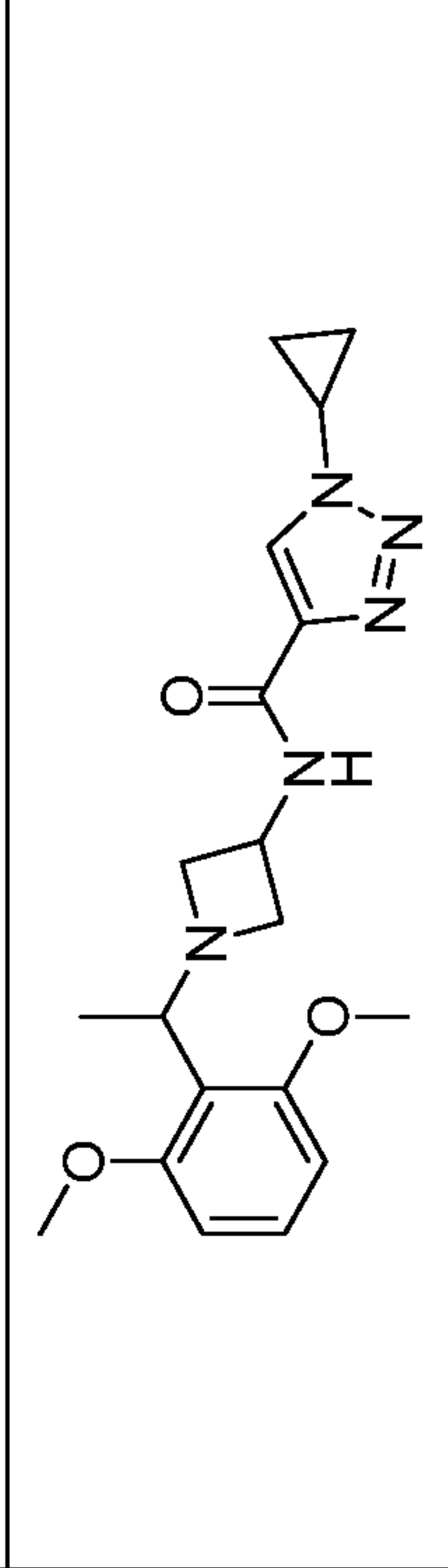
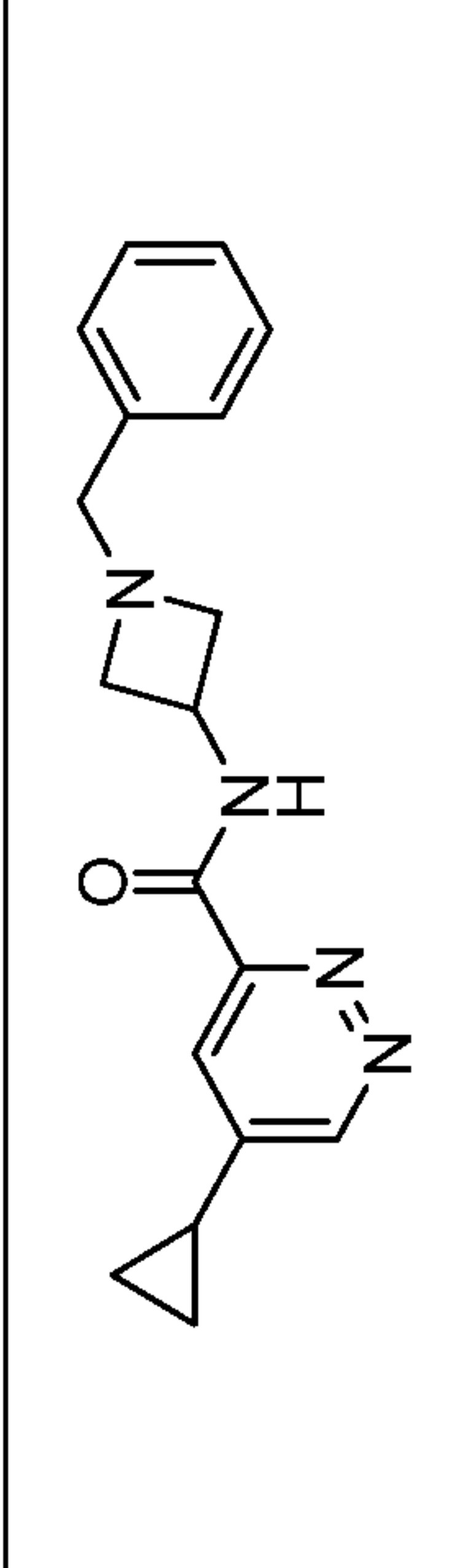
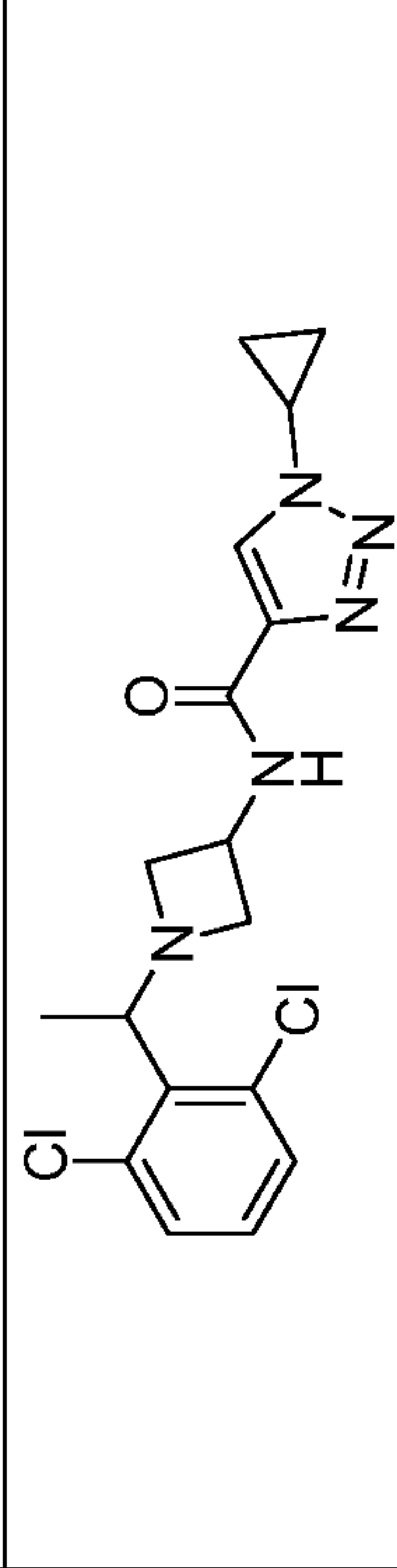
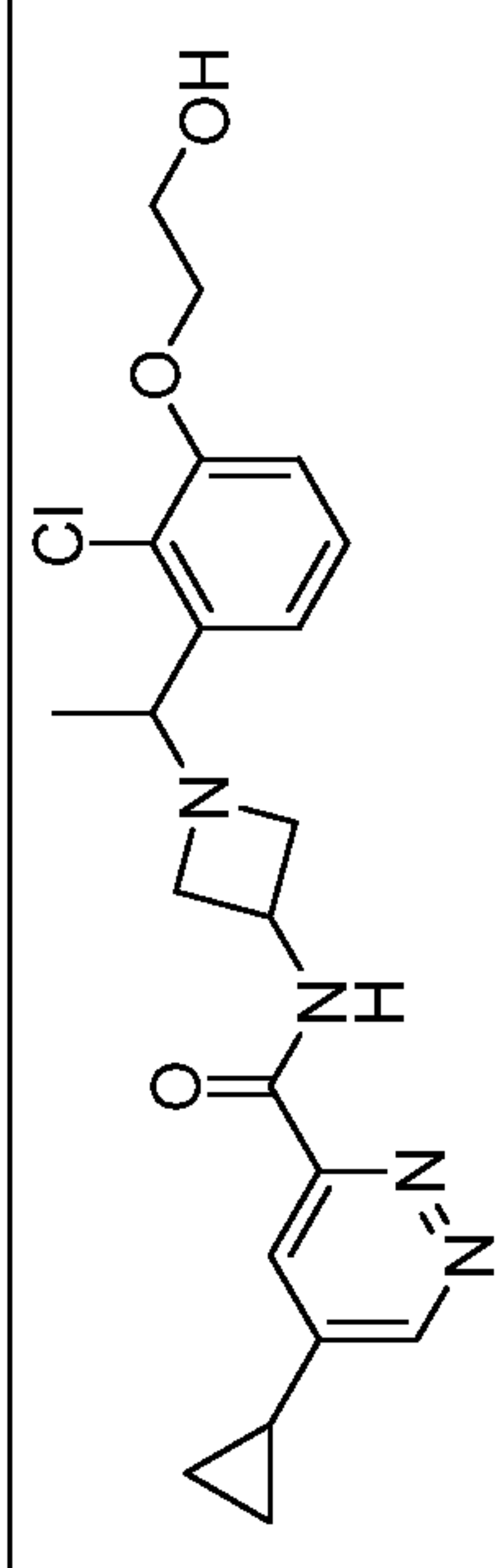
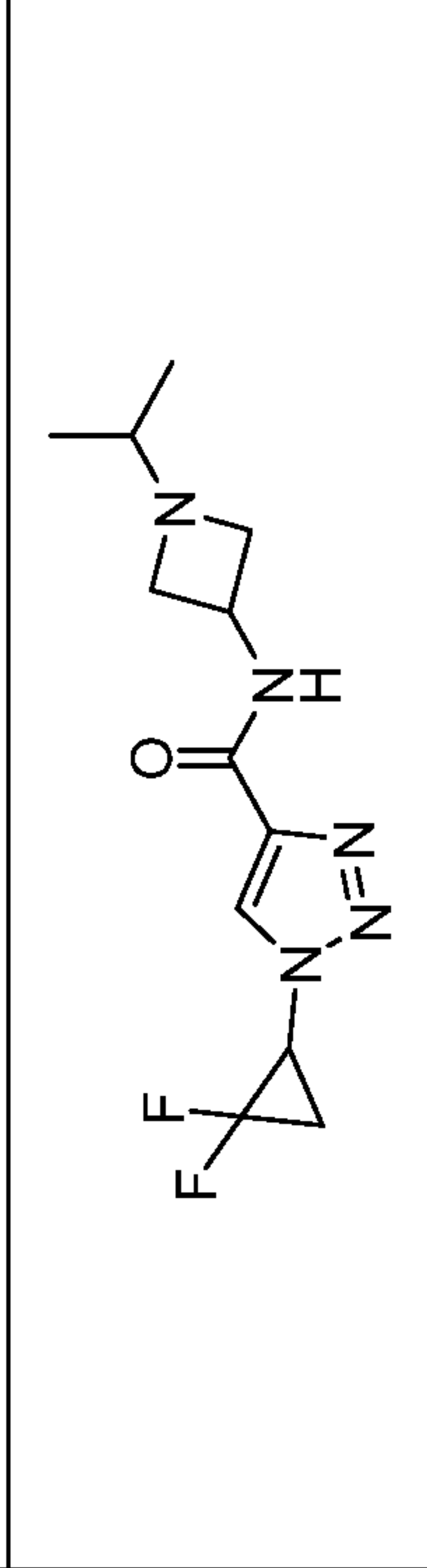
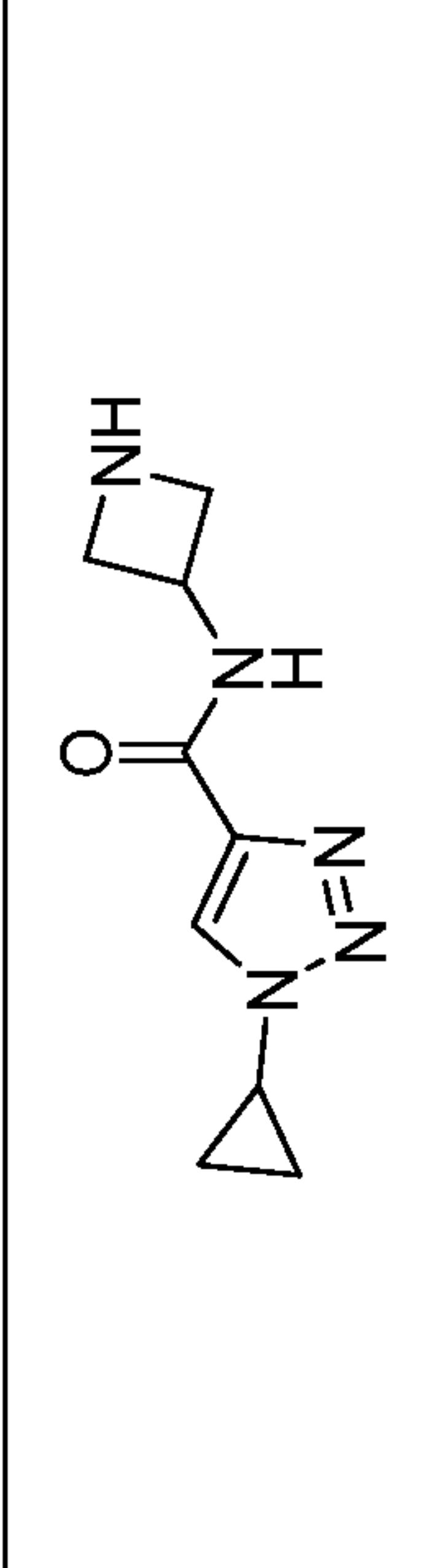
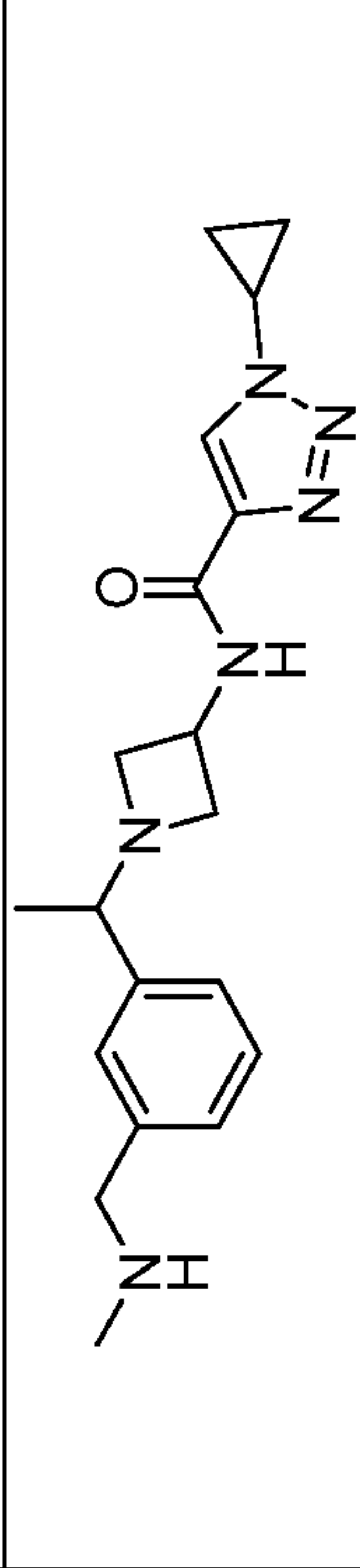
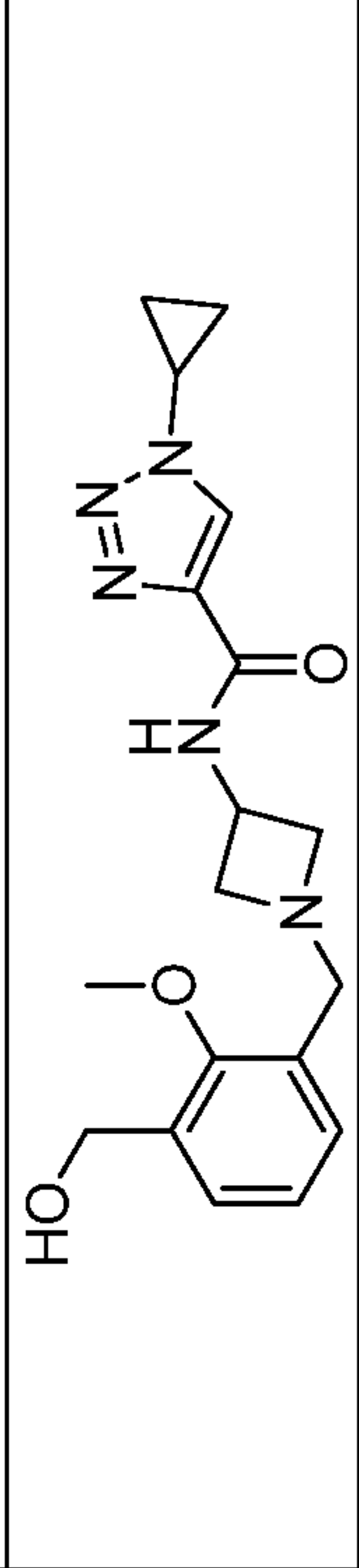
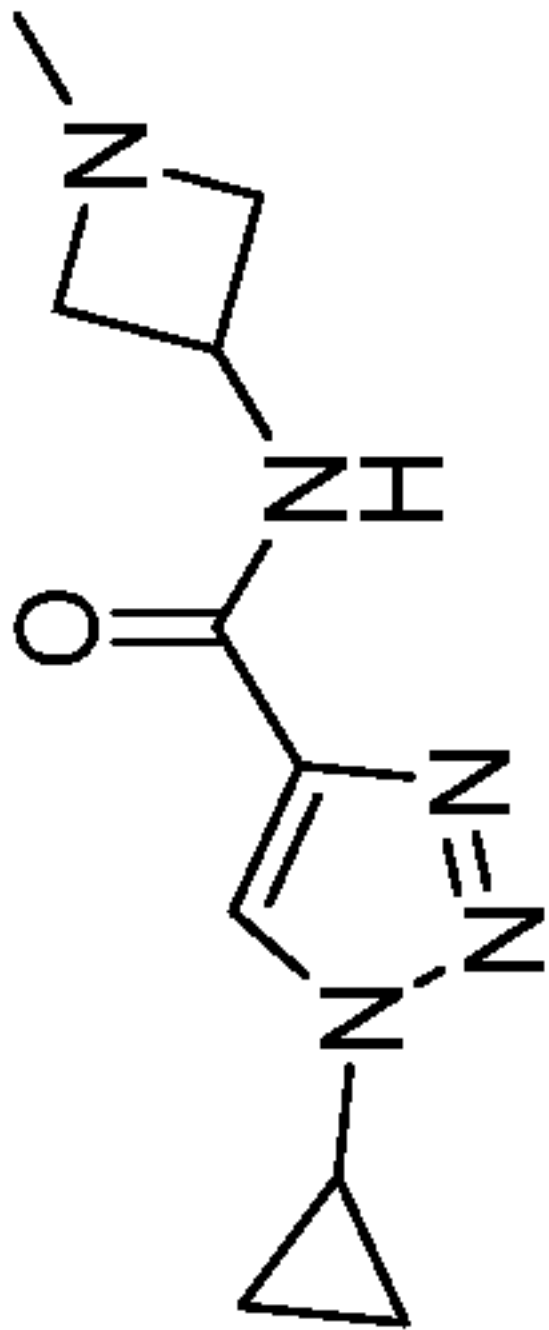
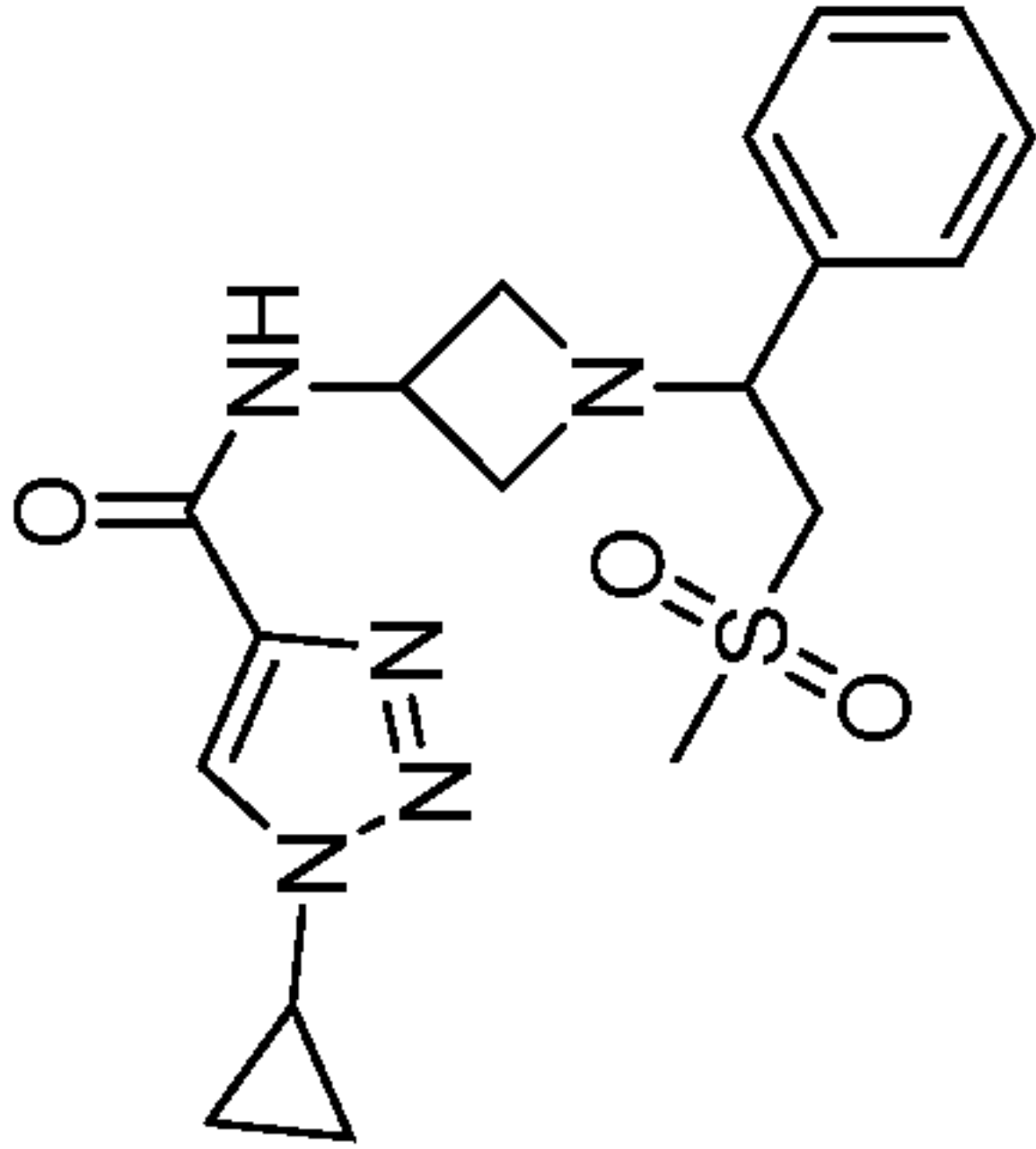
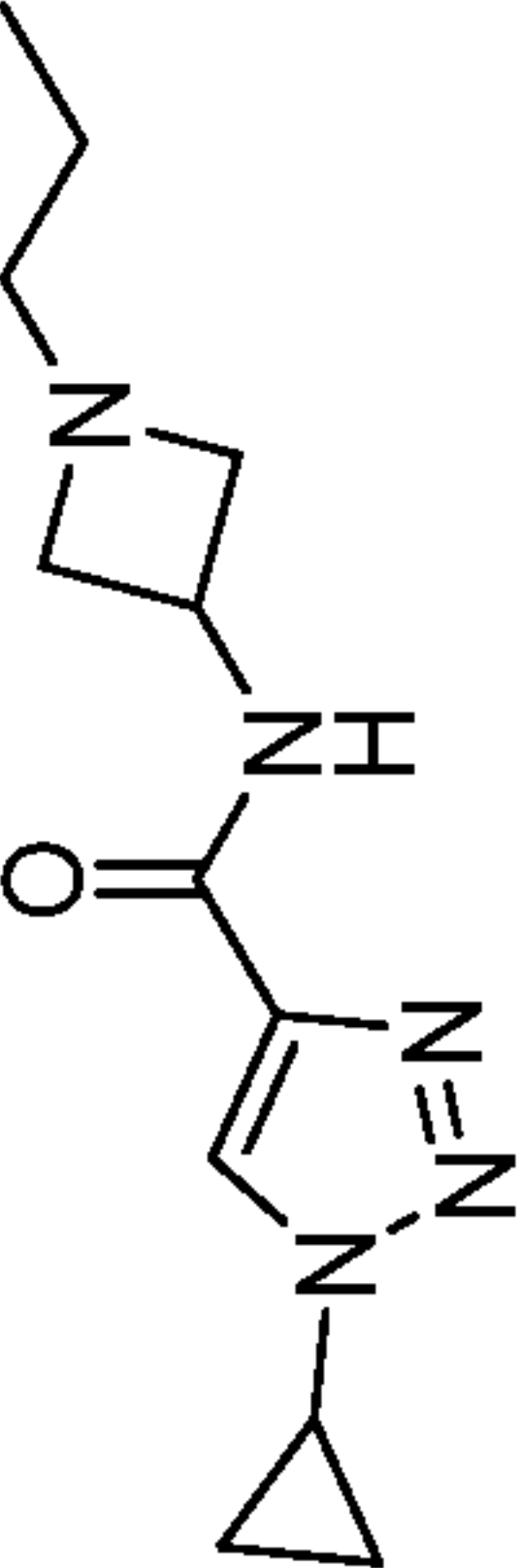
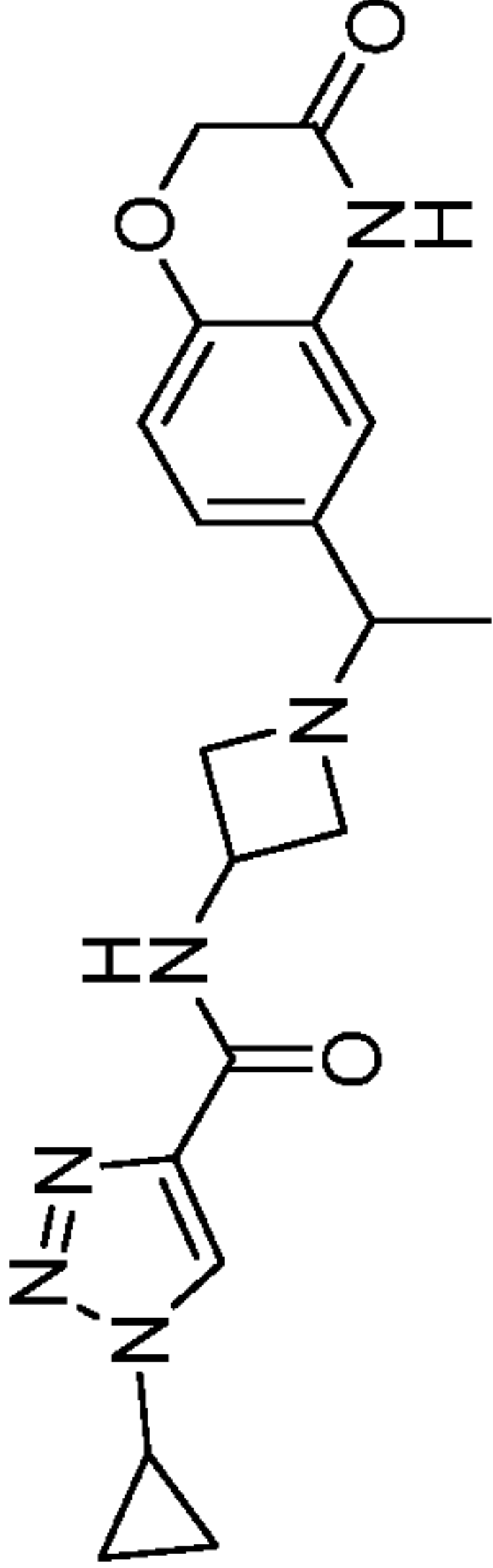
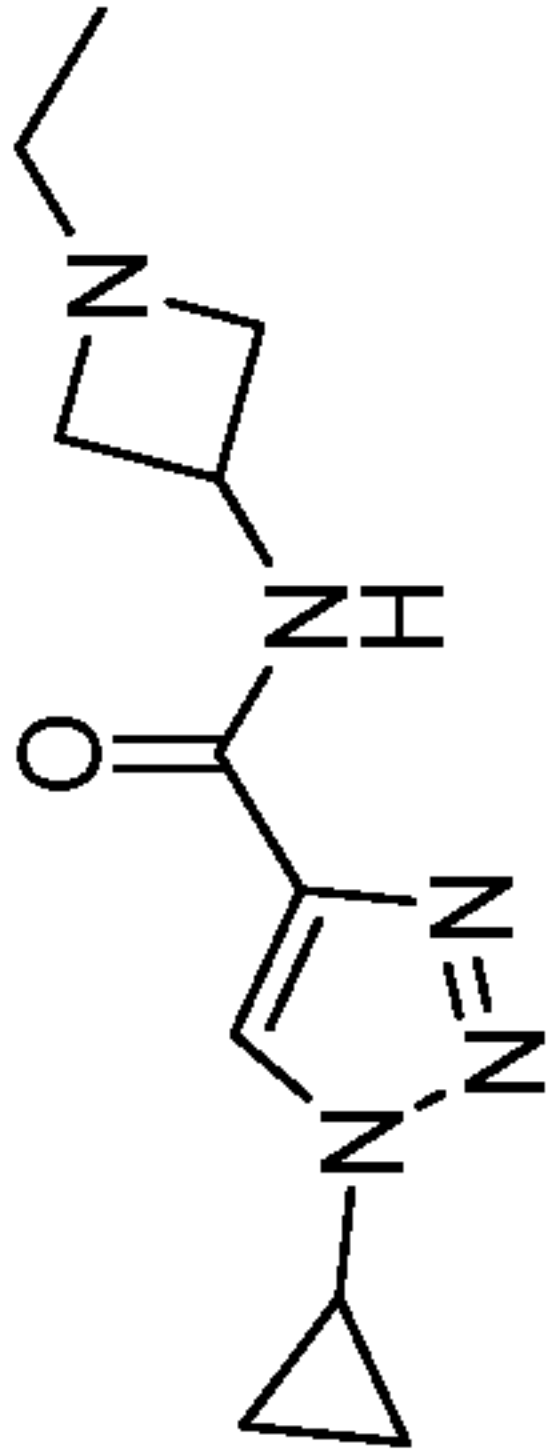
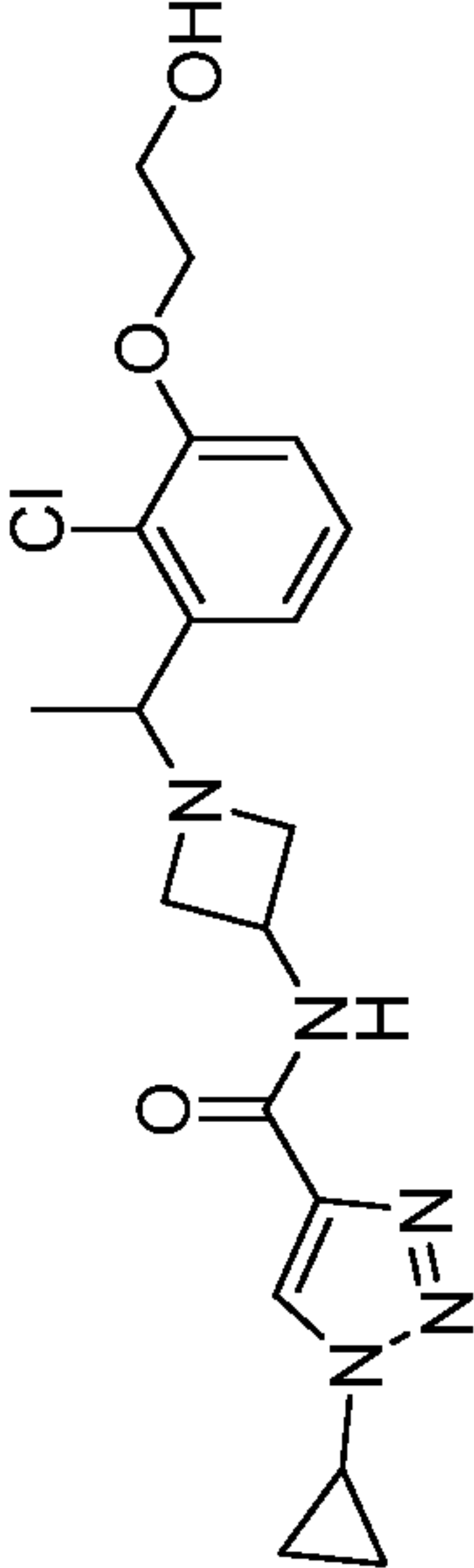
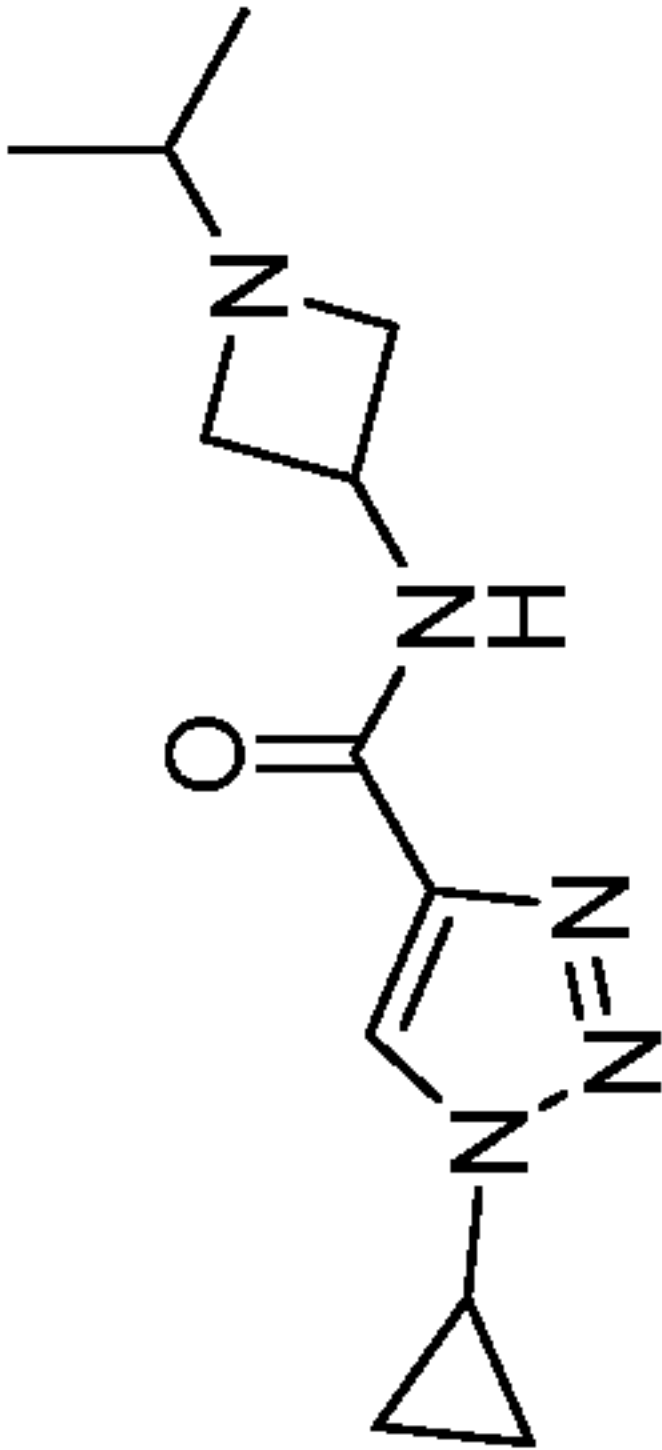
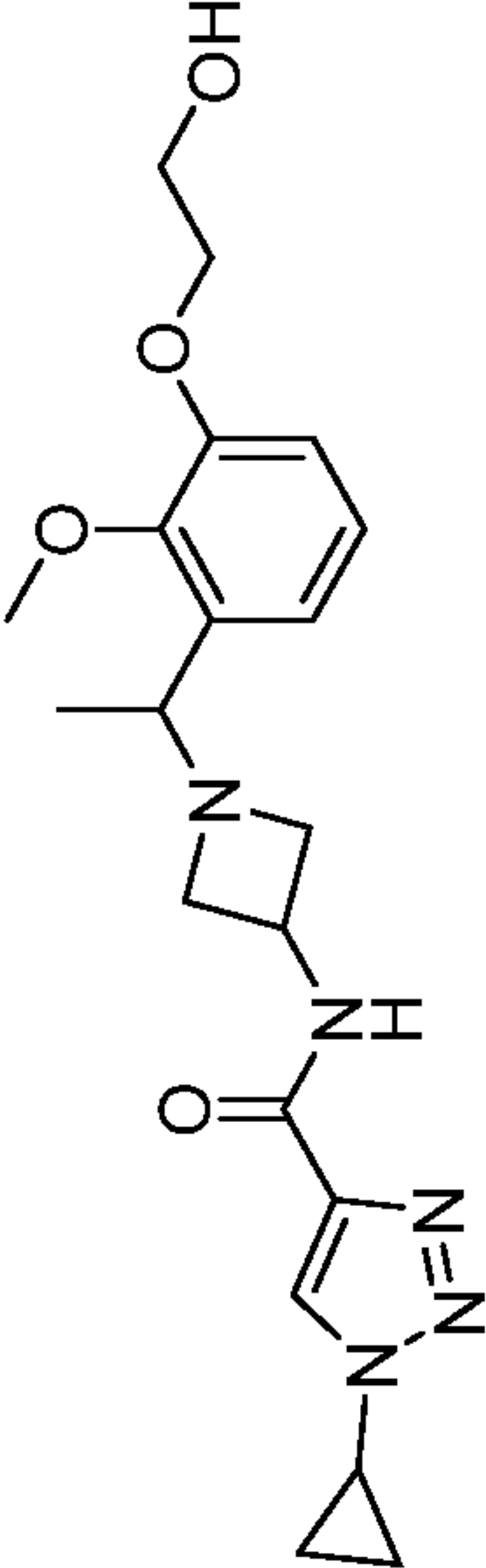
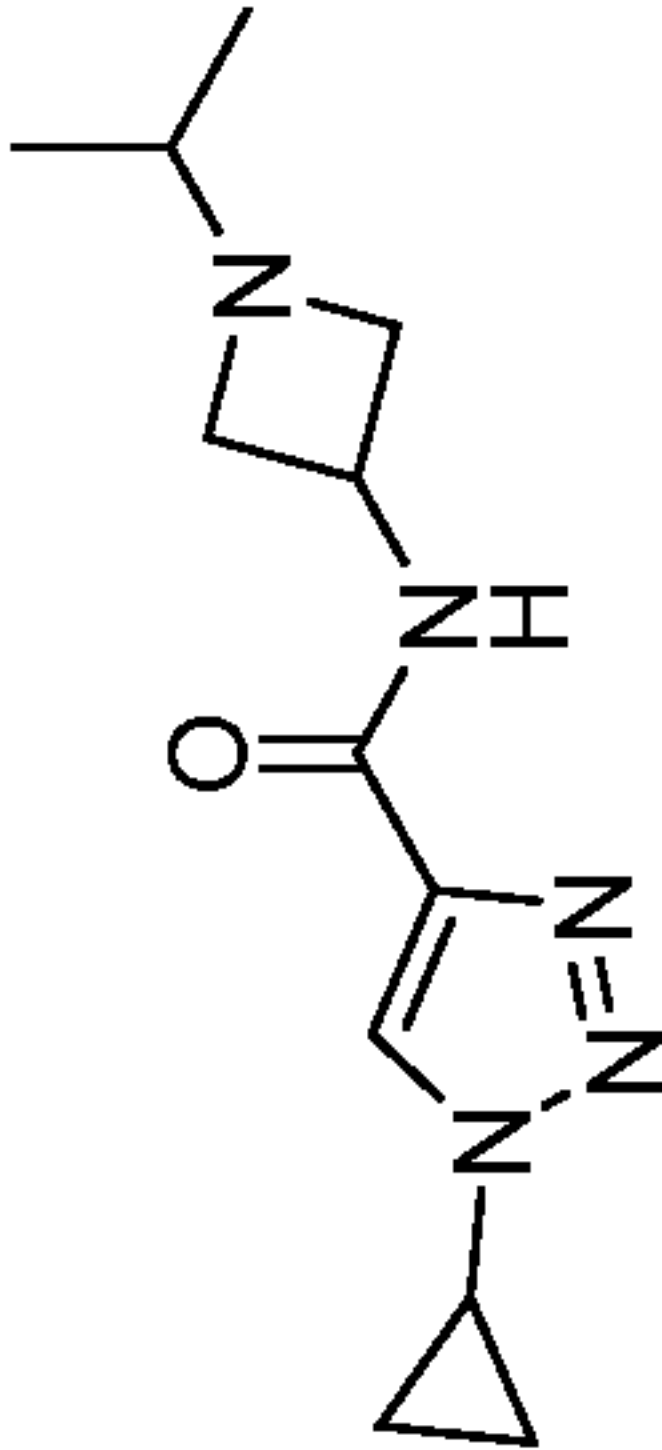
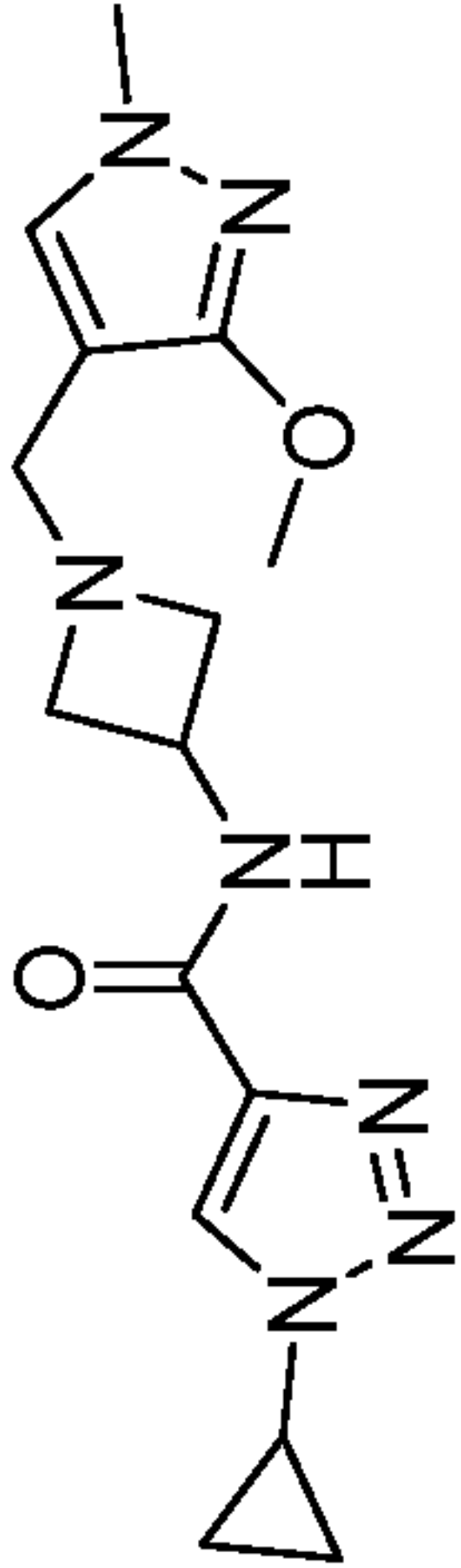
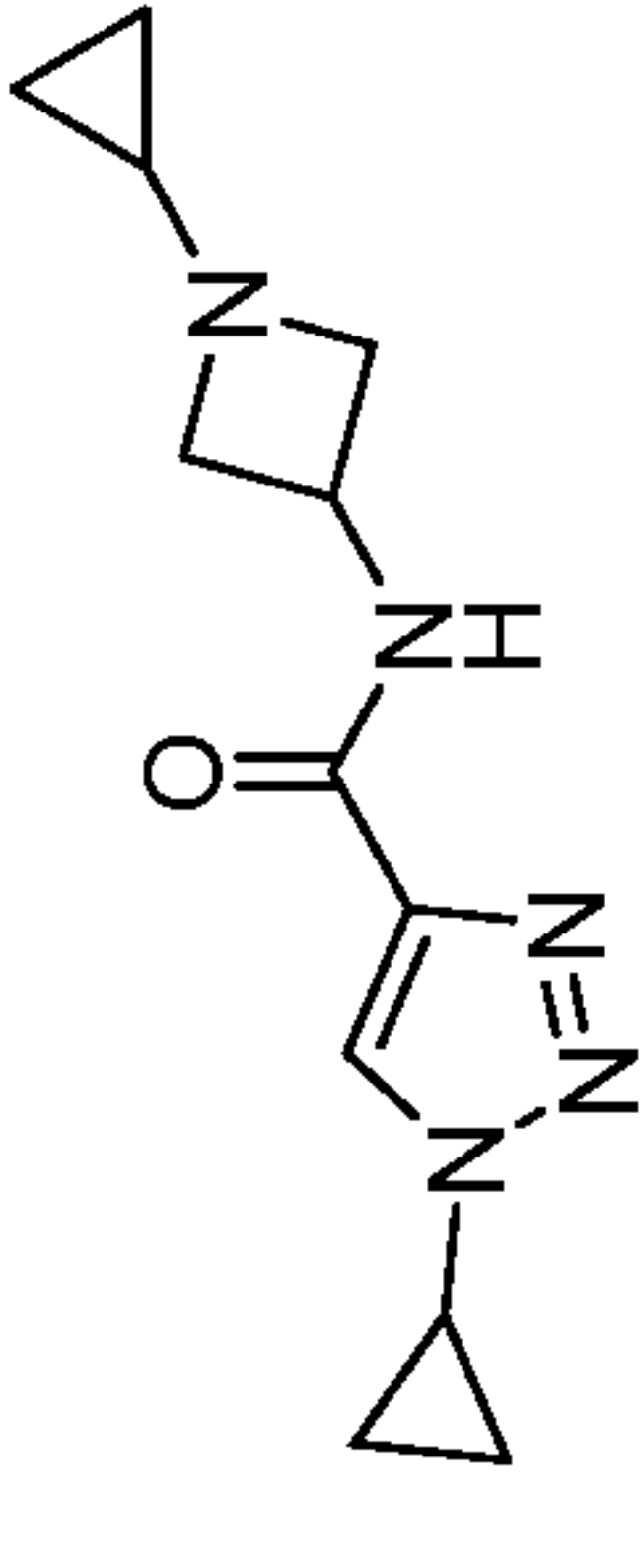
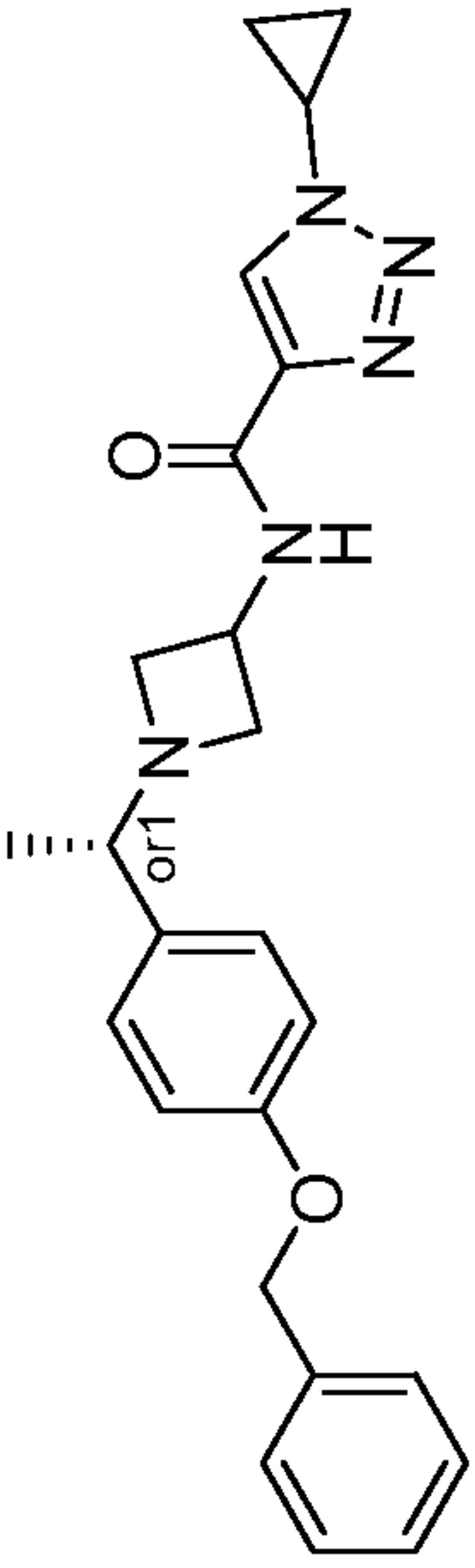
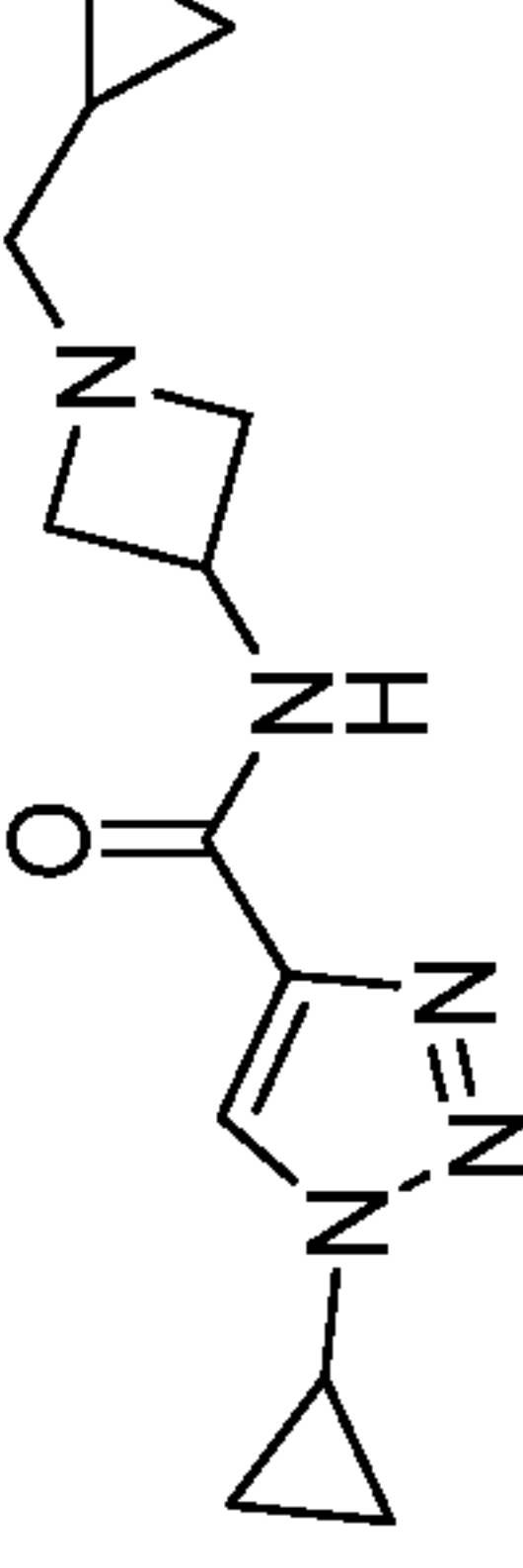
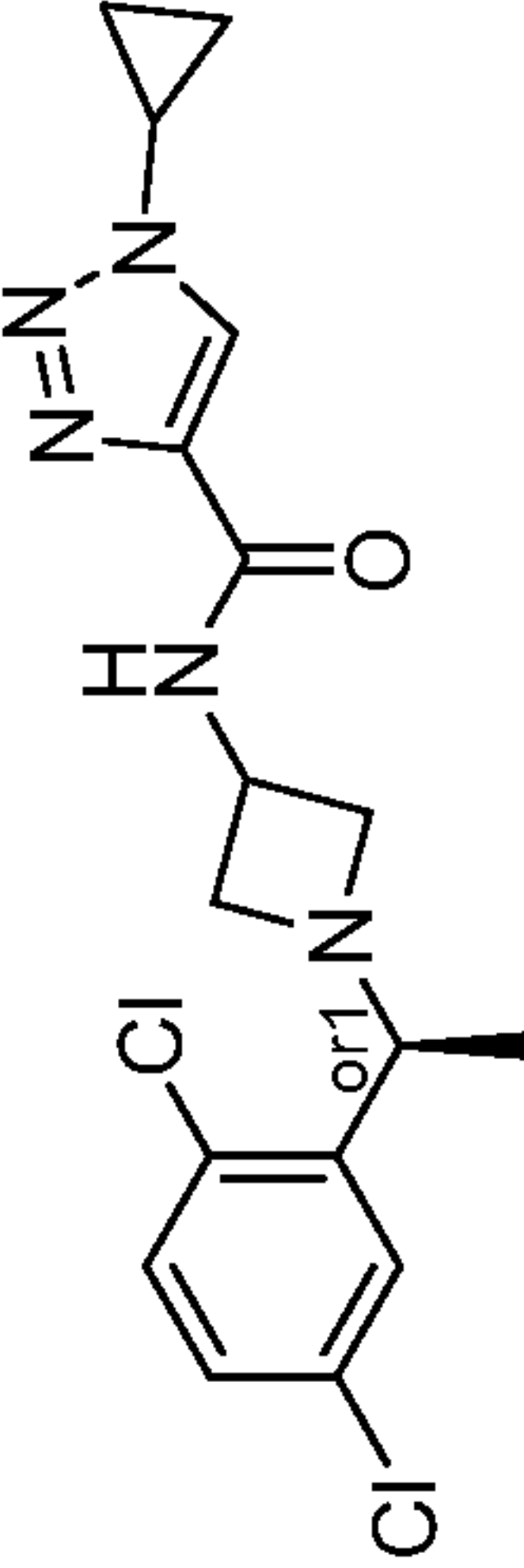
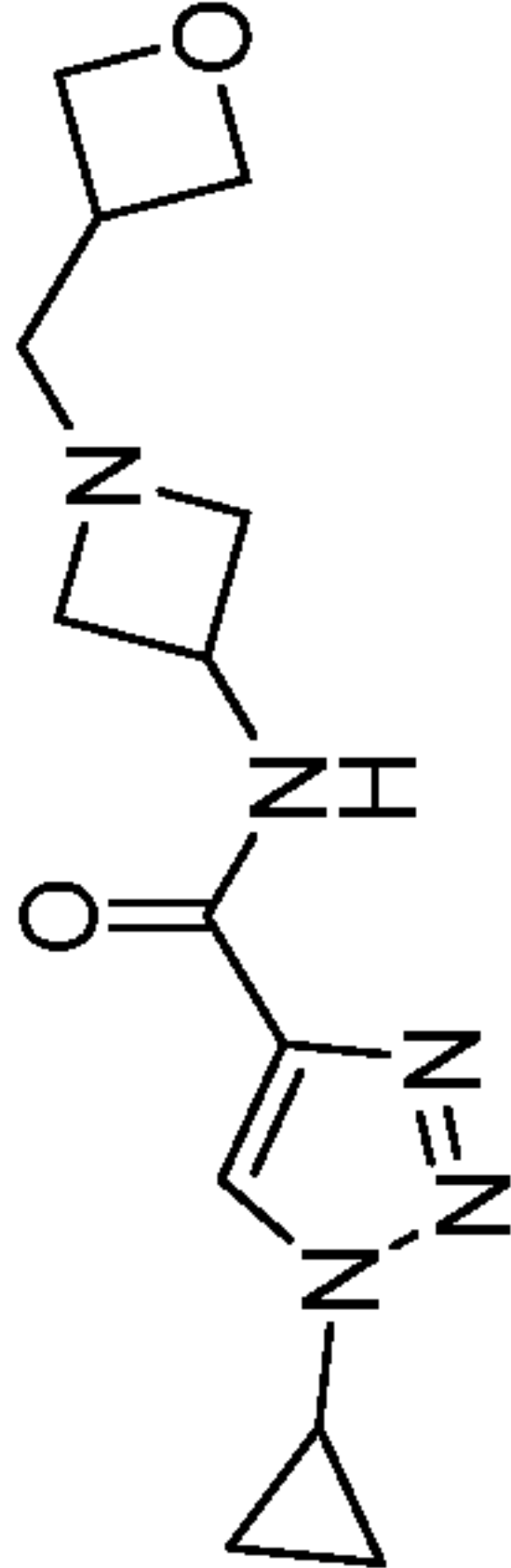
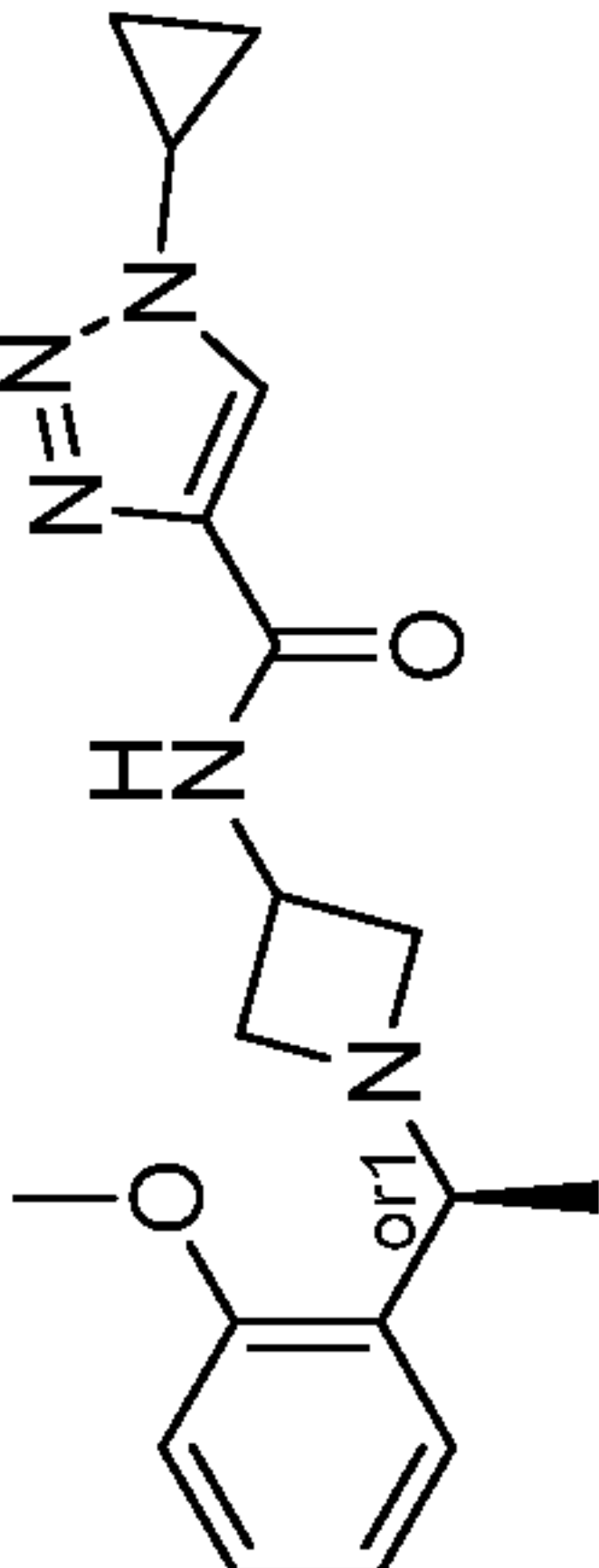
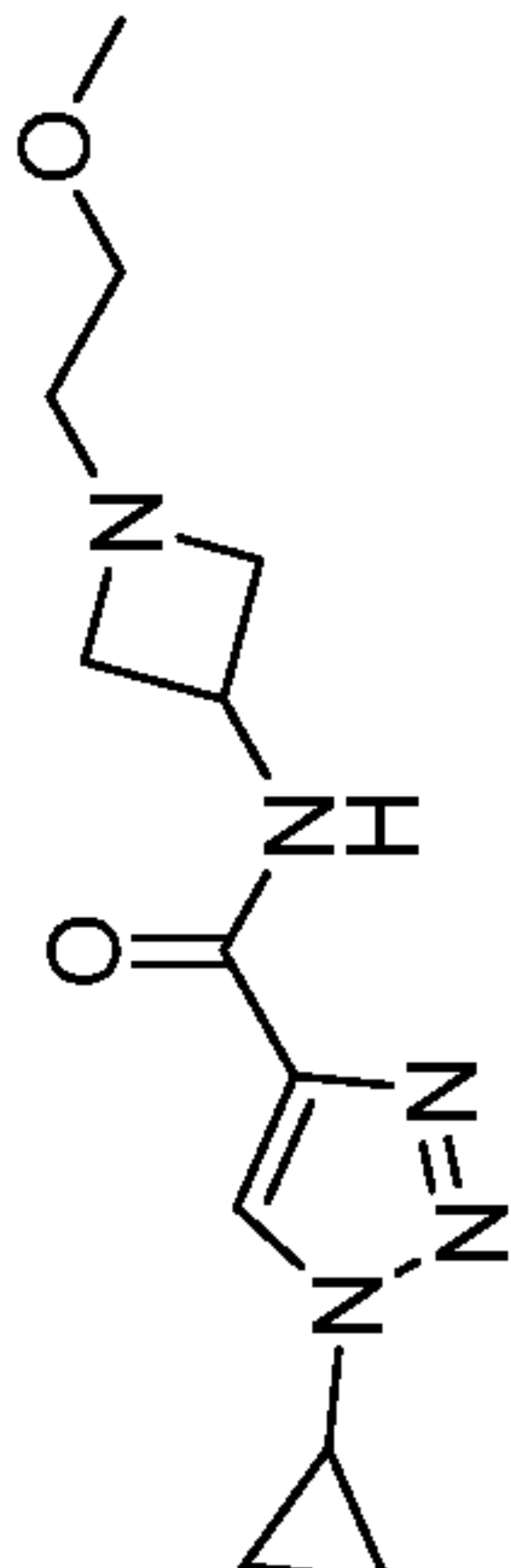
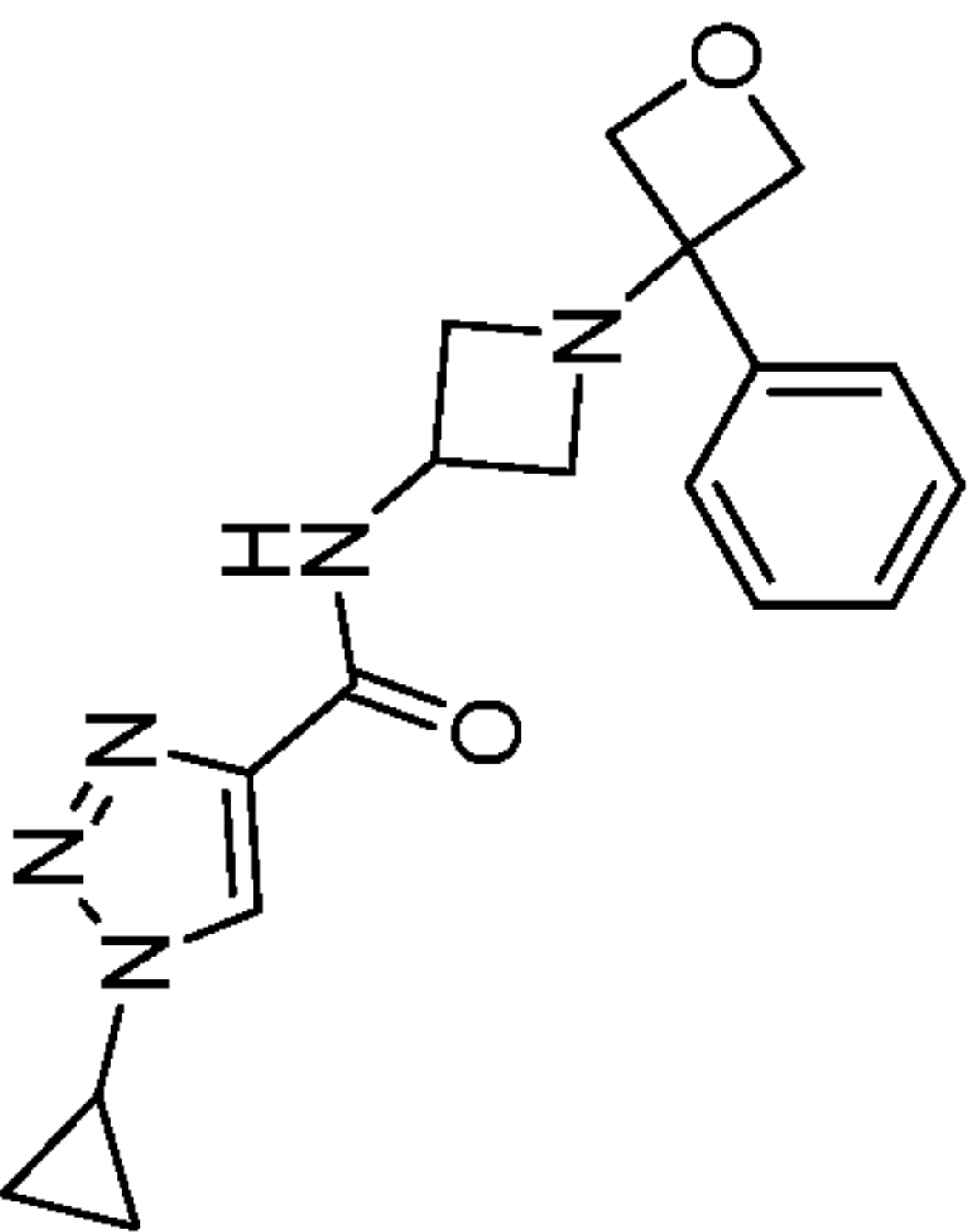
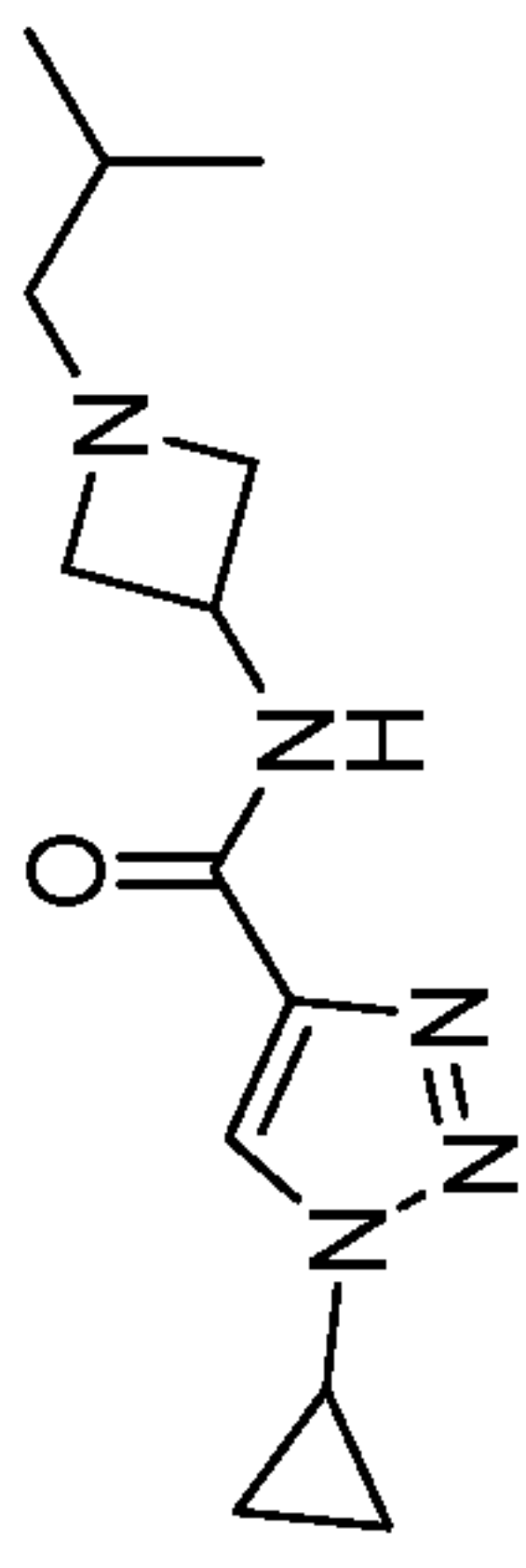
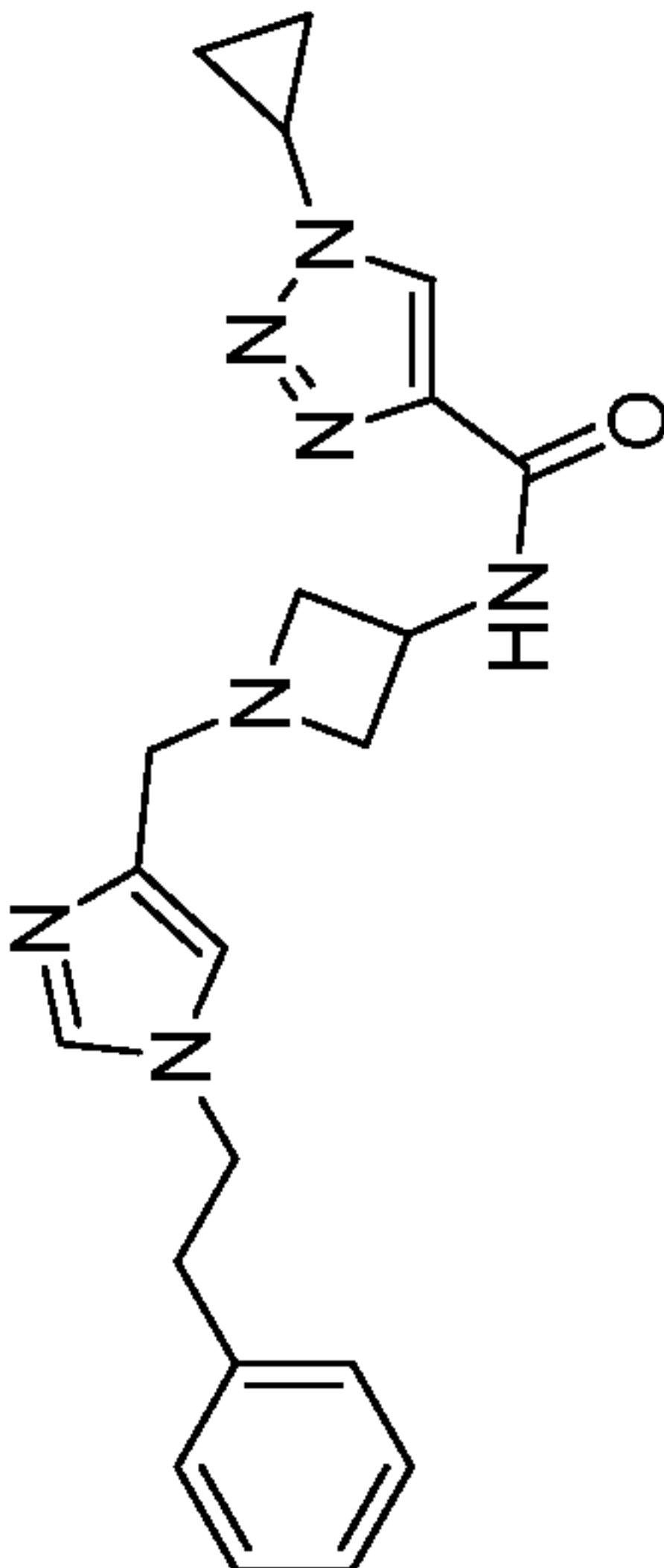
607		HCl	642		HCl
608		TFA	643		None
609		HCl	644		HCl

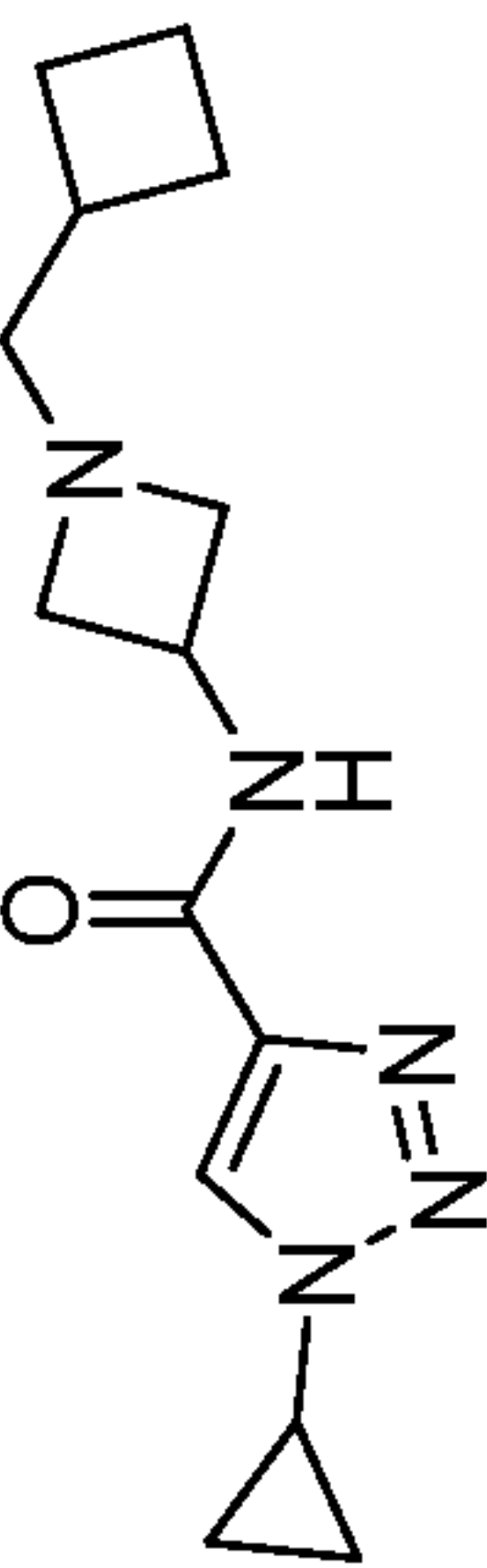
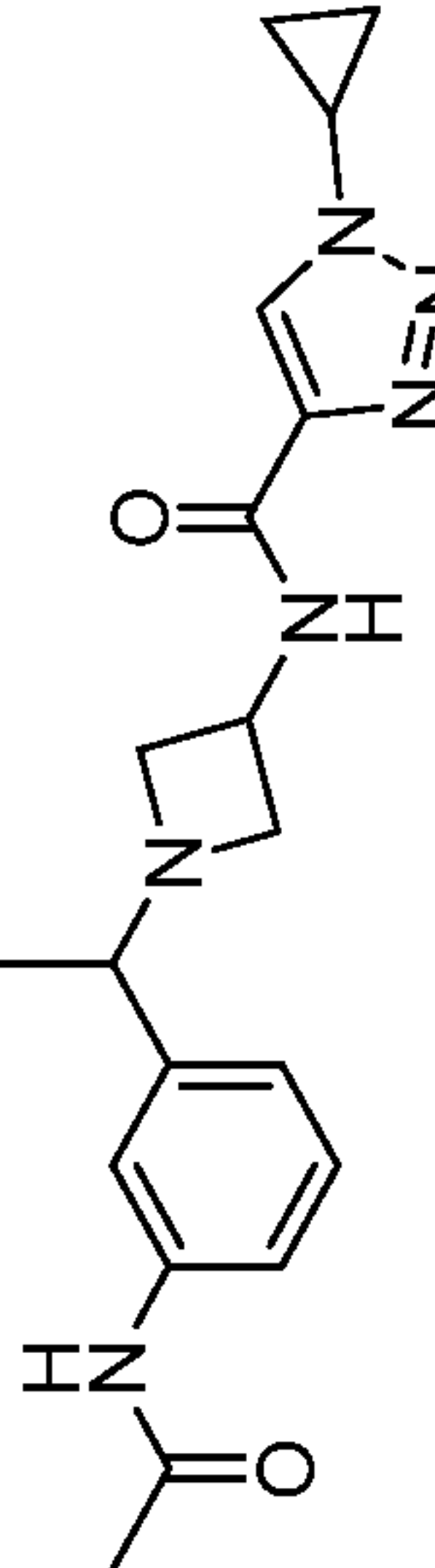
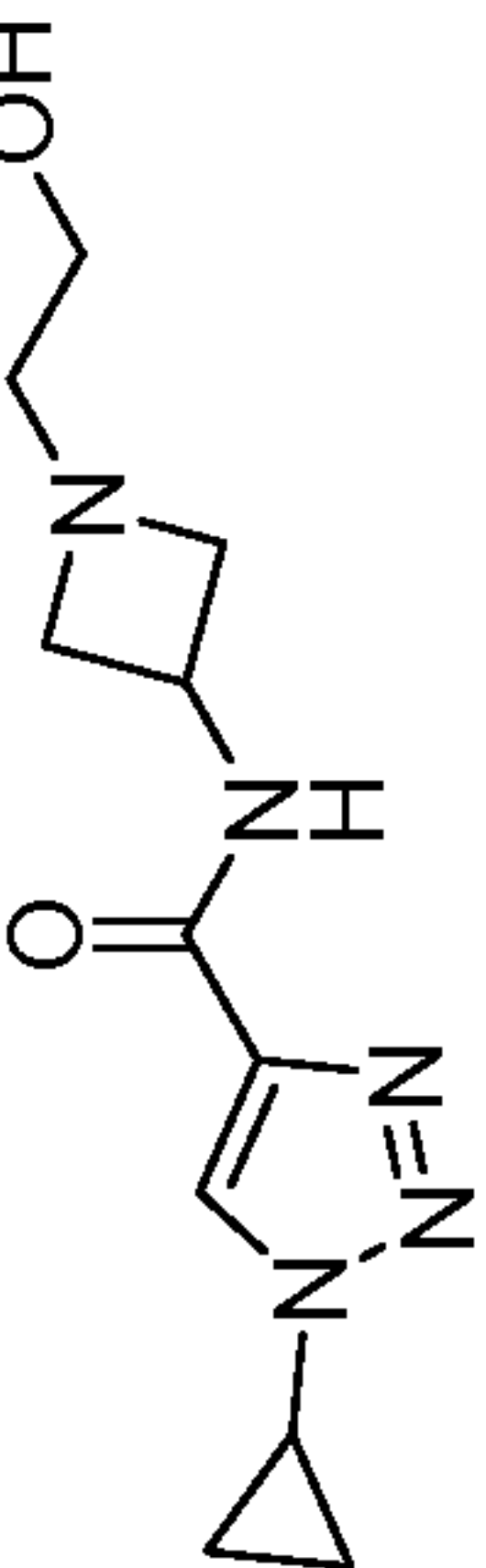
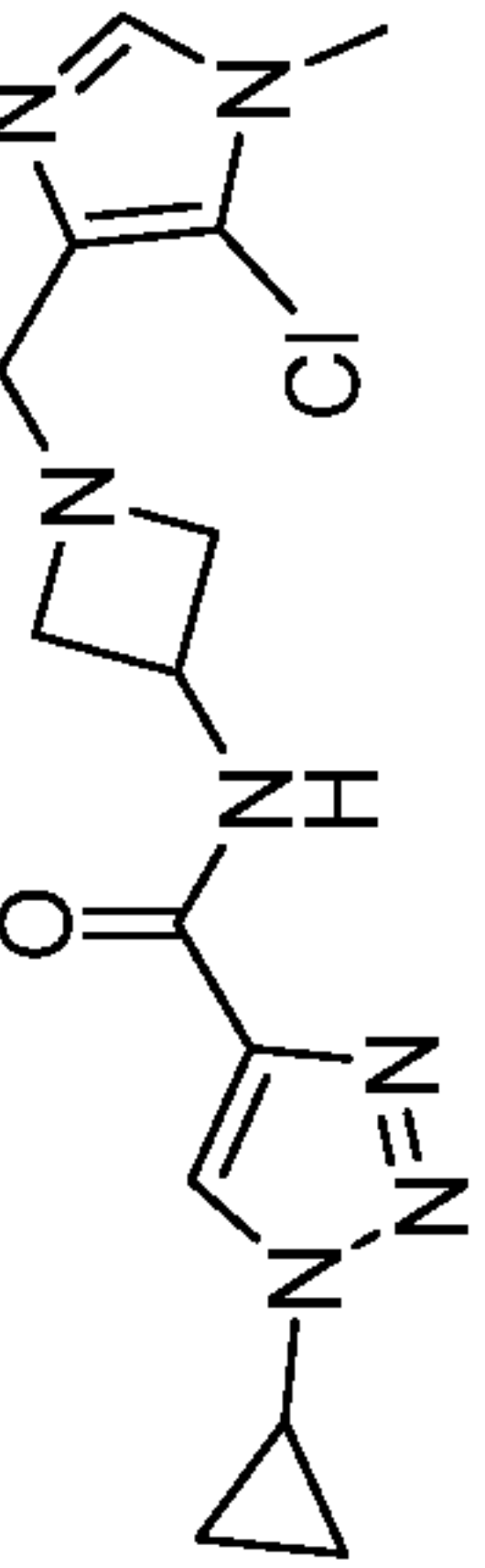
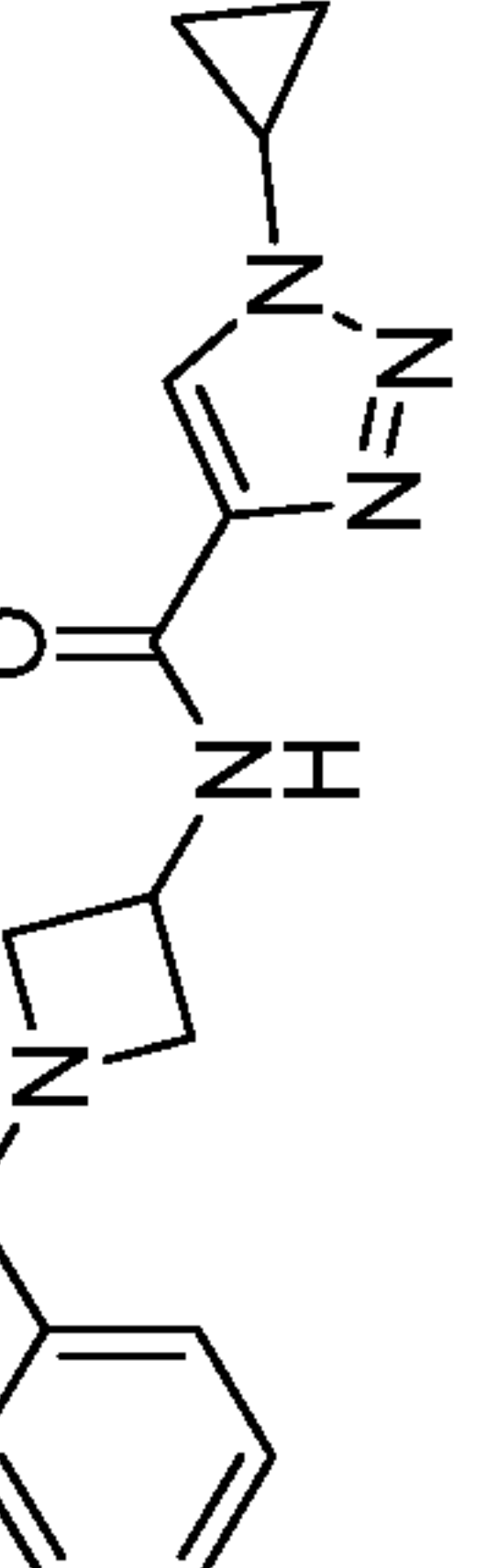
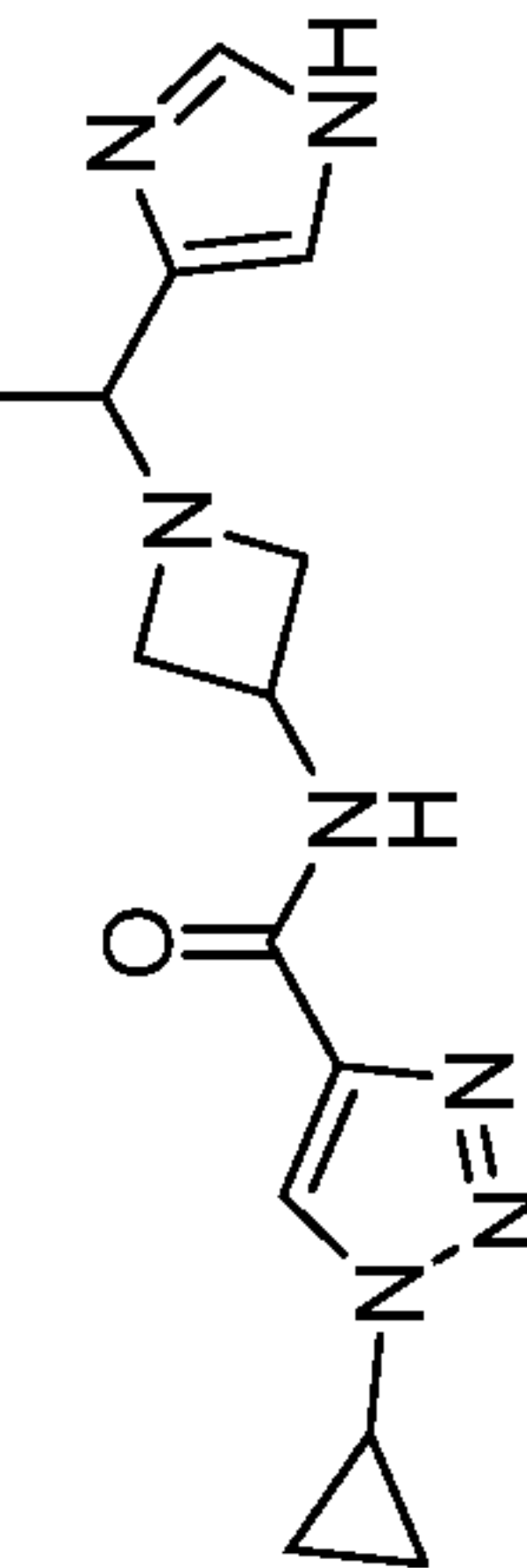
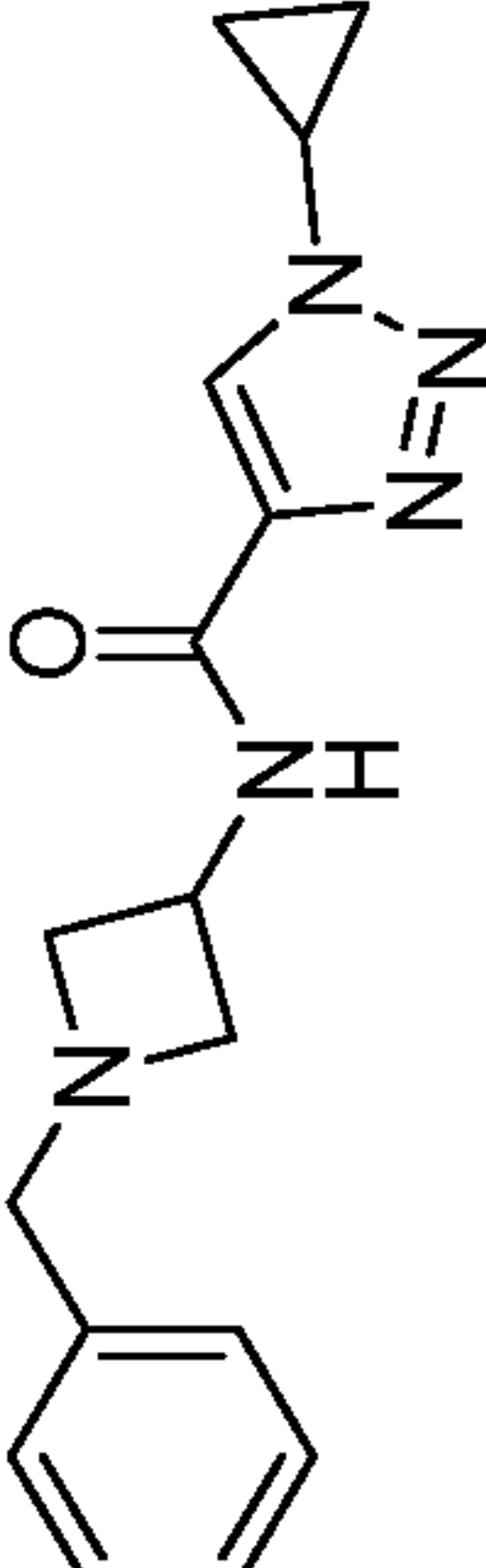
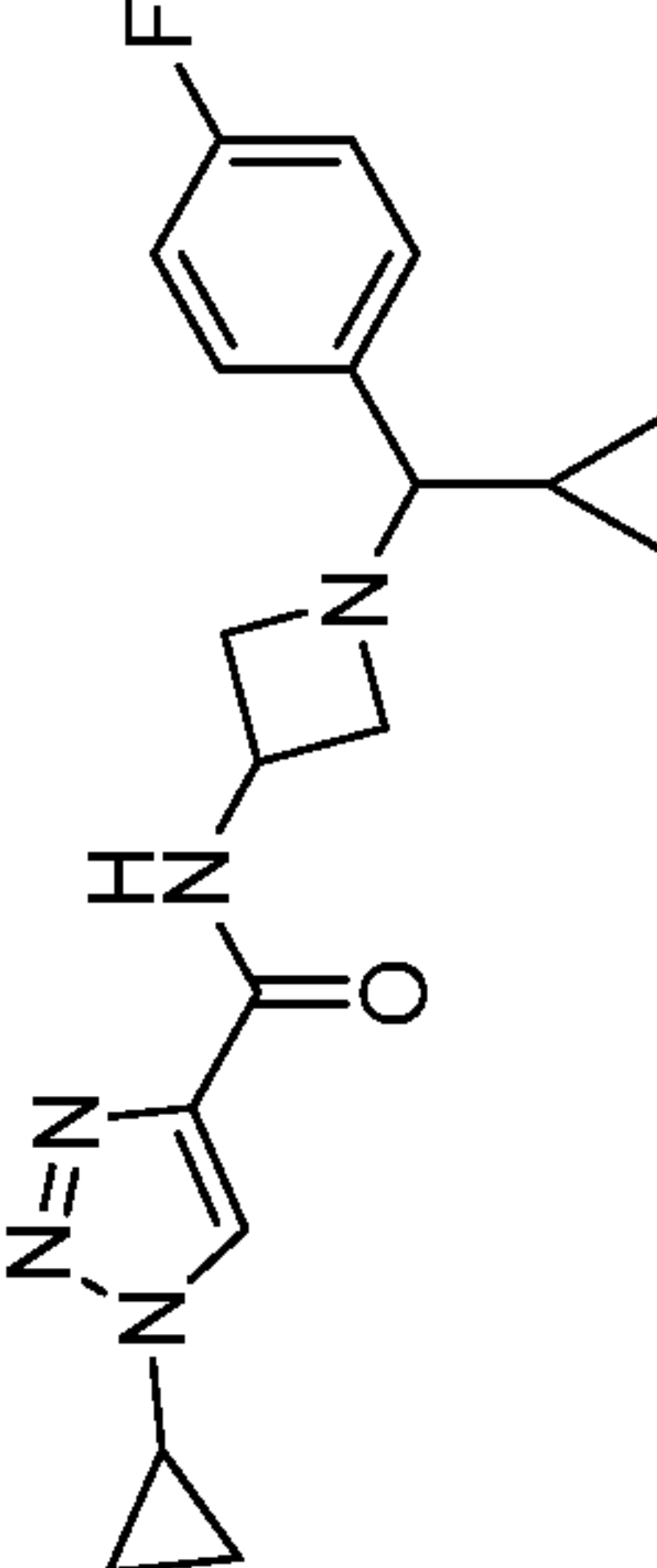
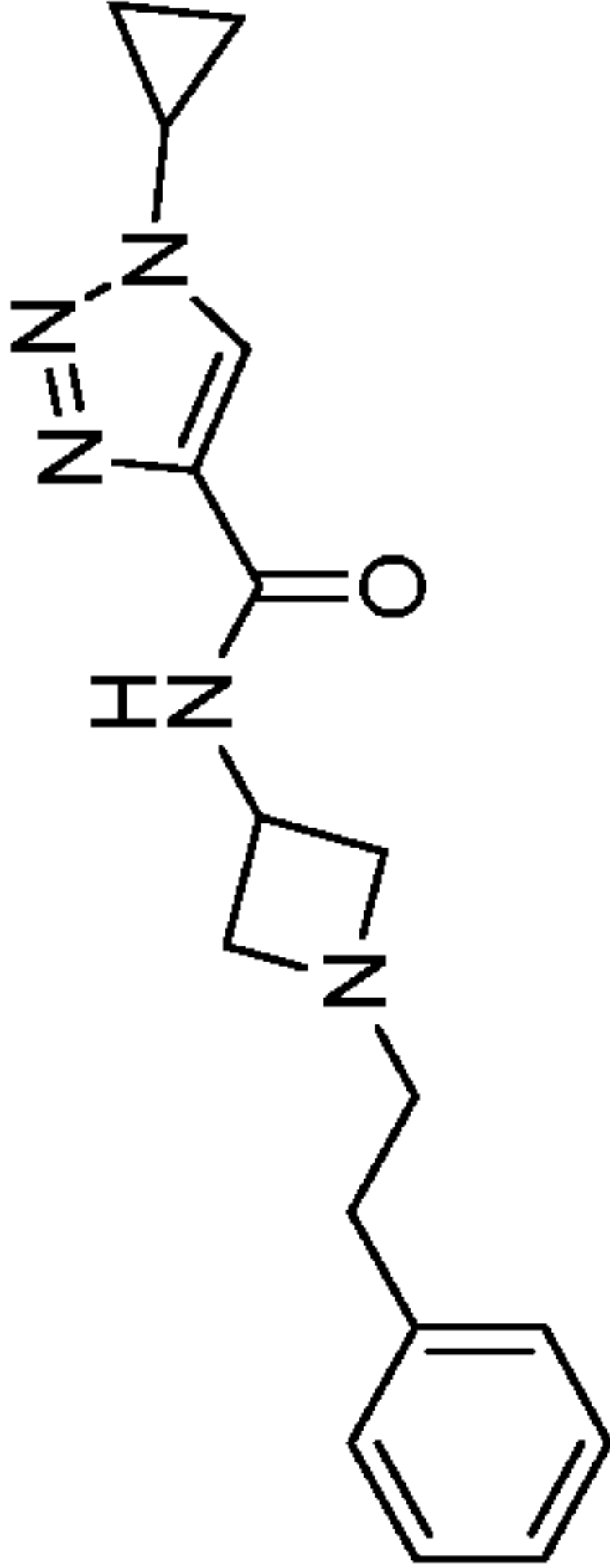
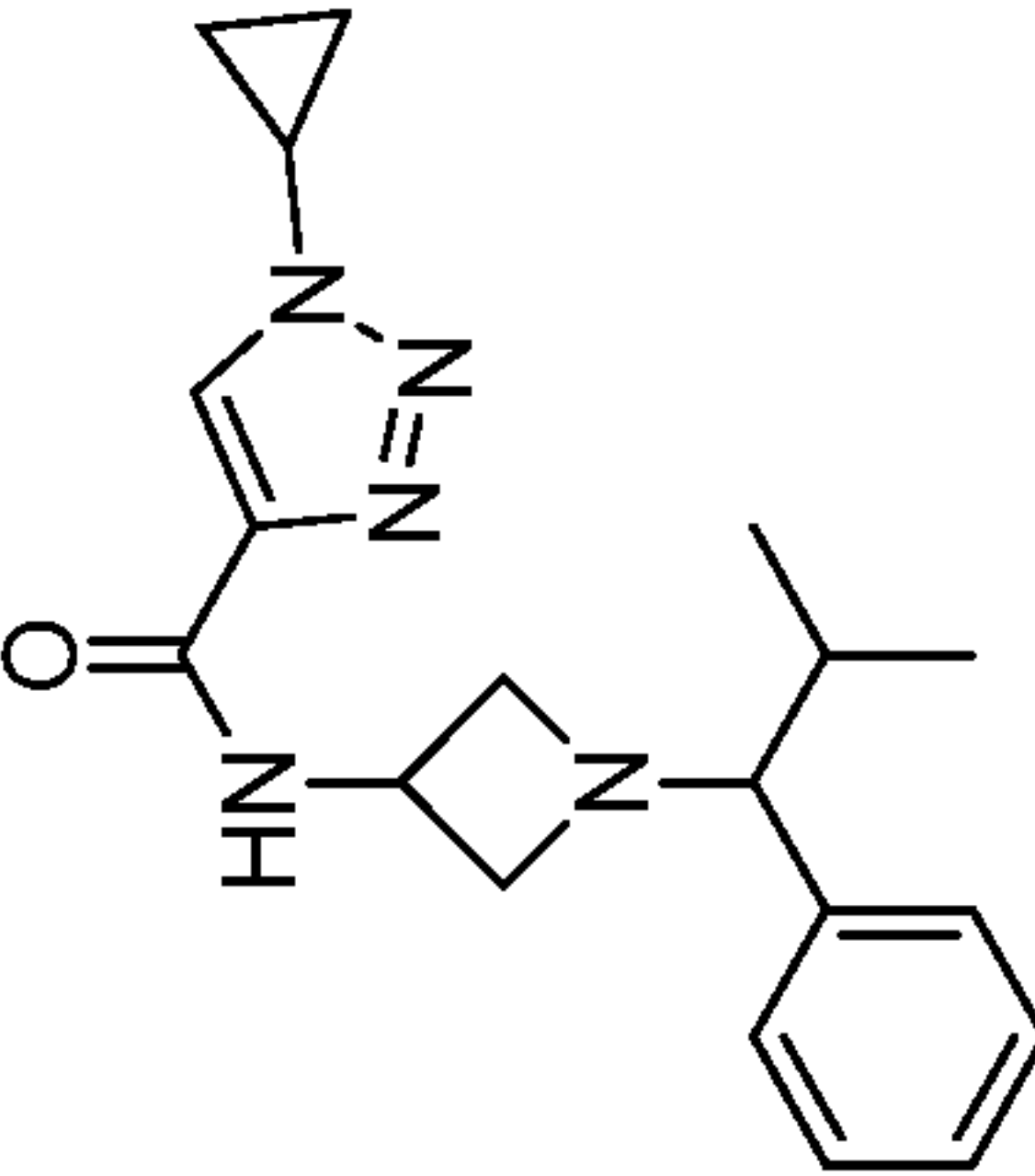
Table 4

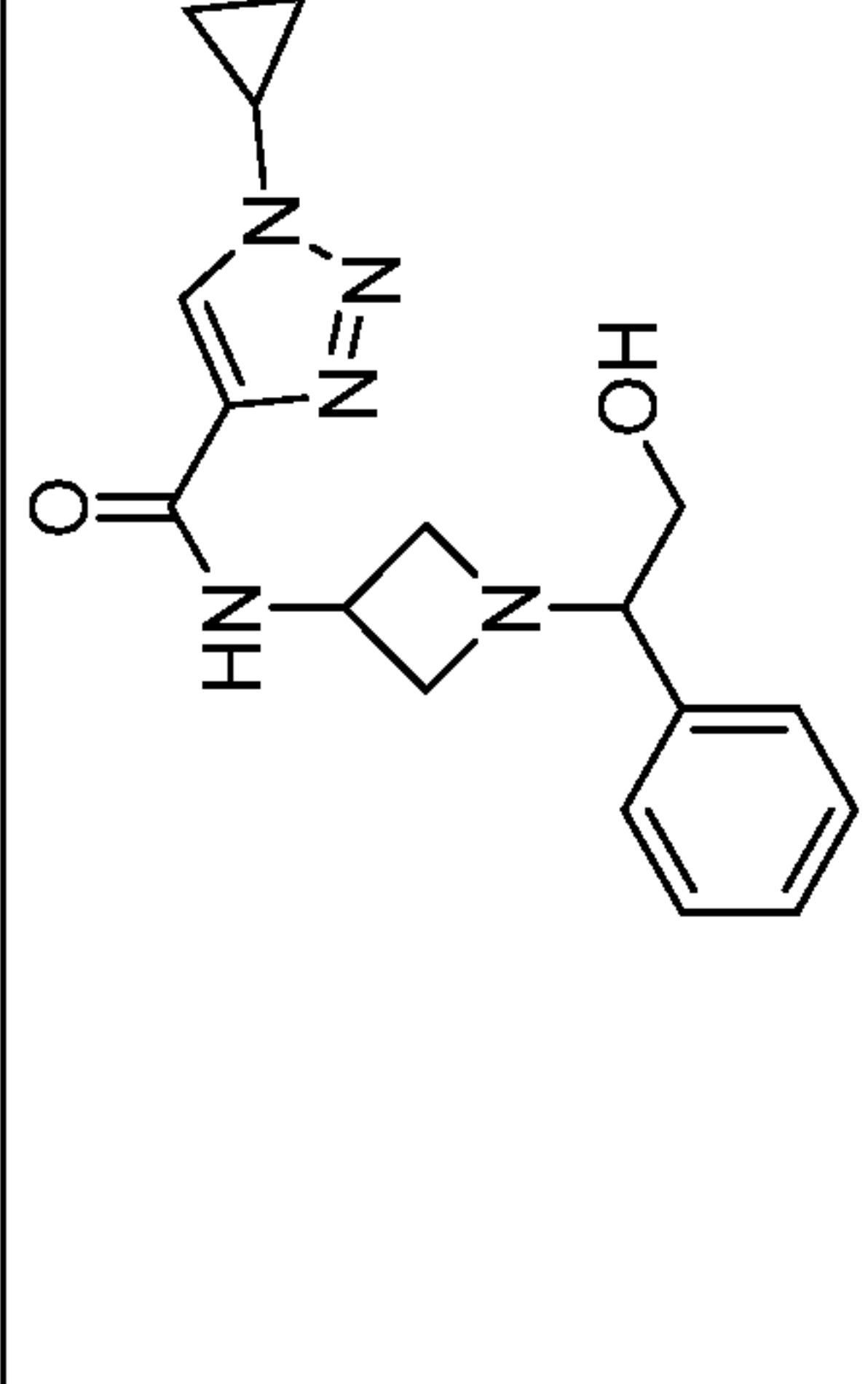
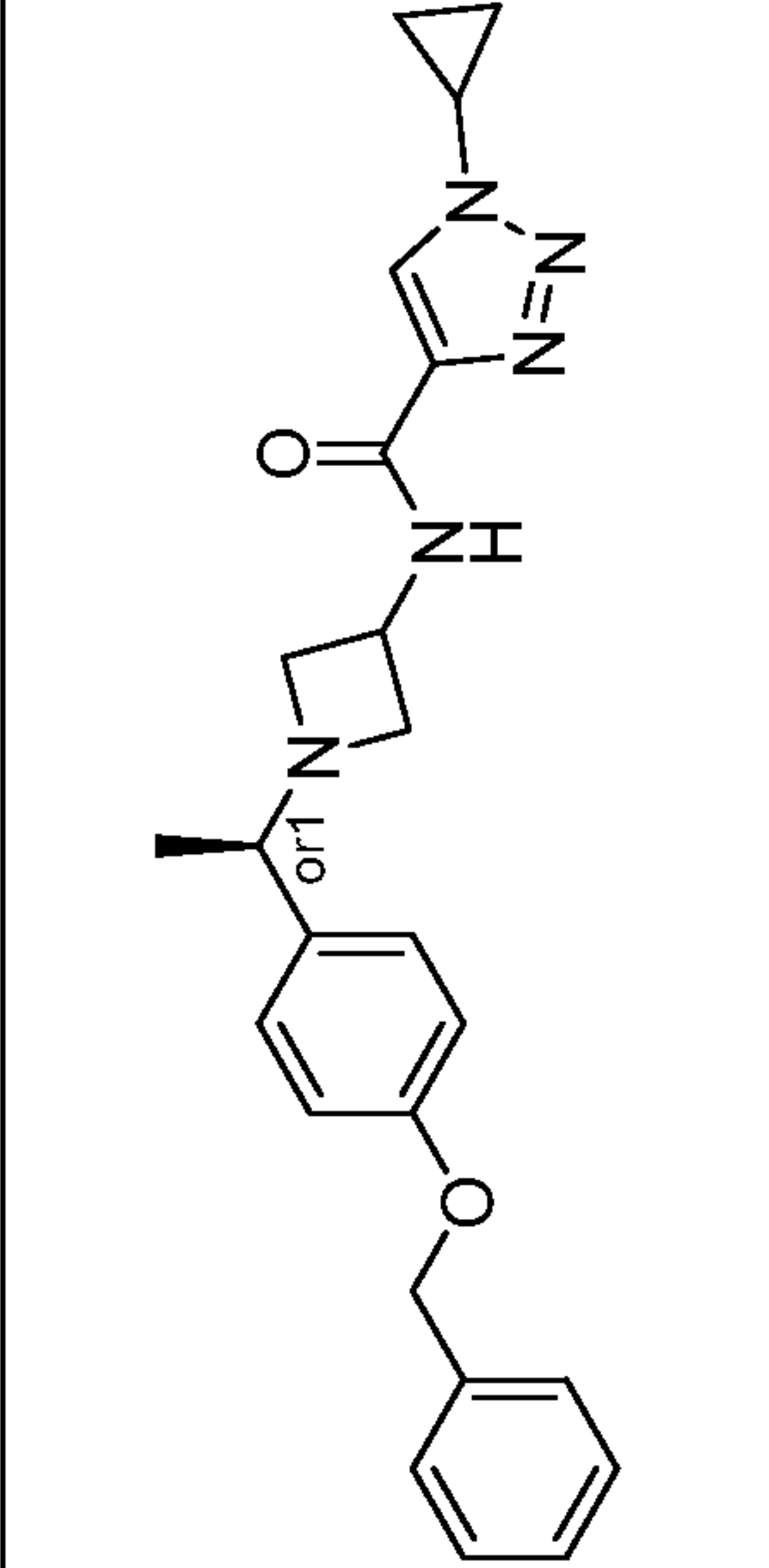
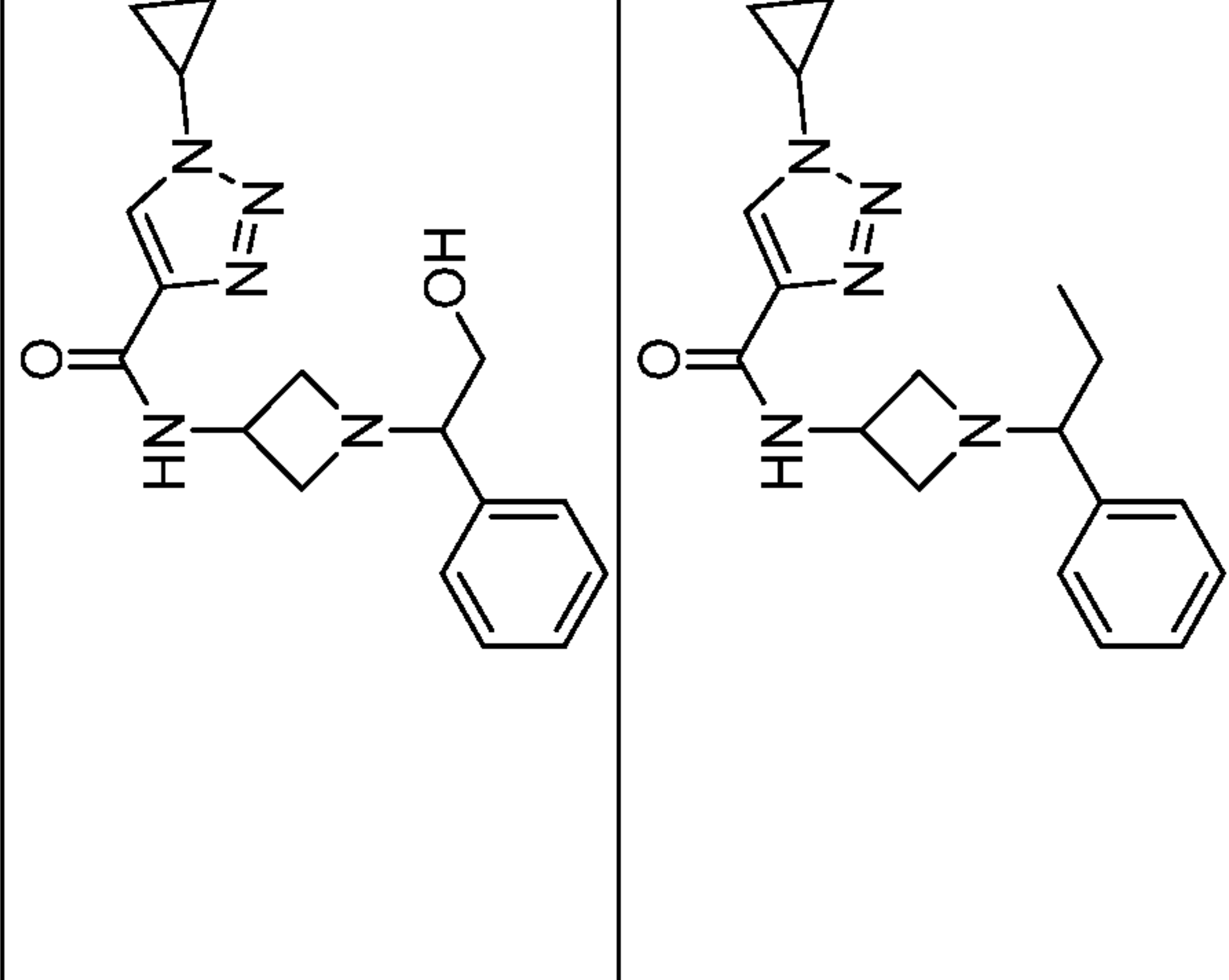
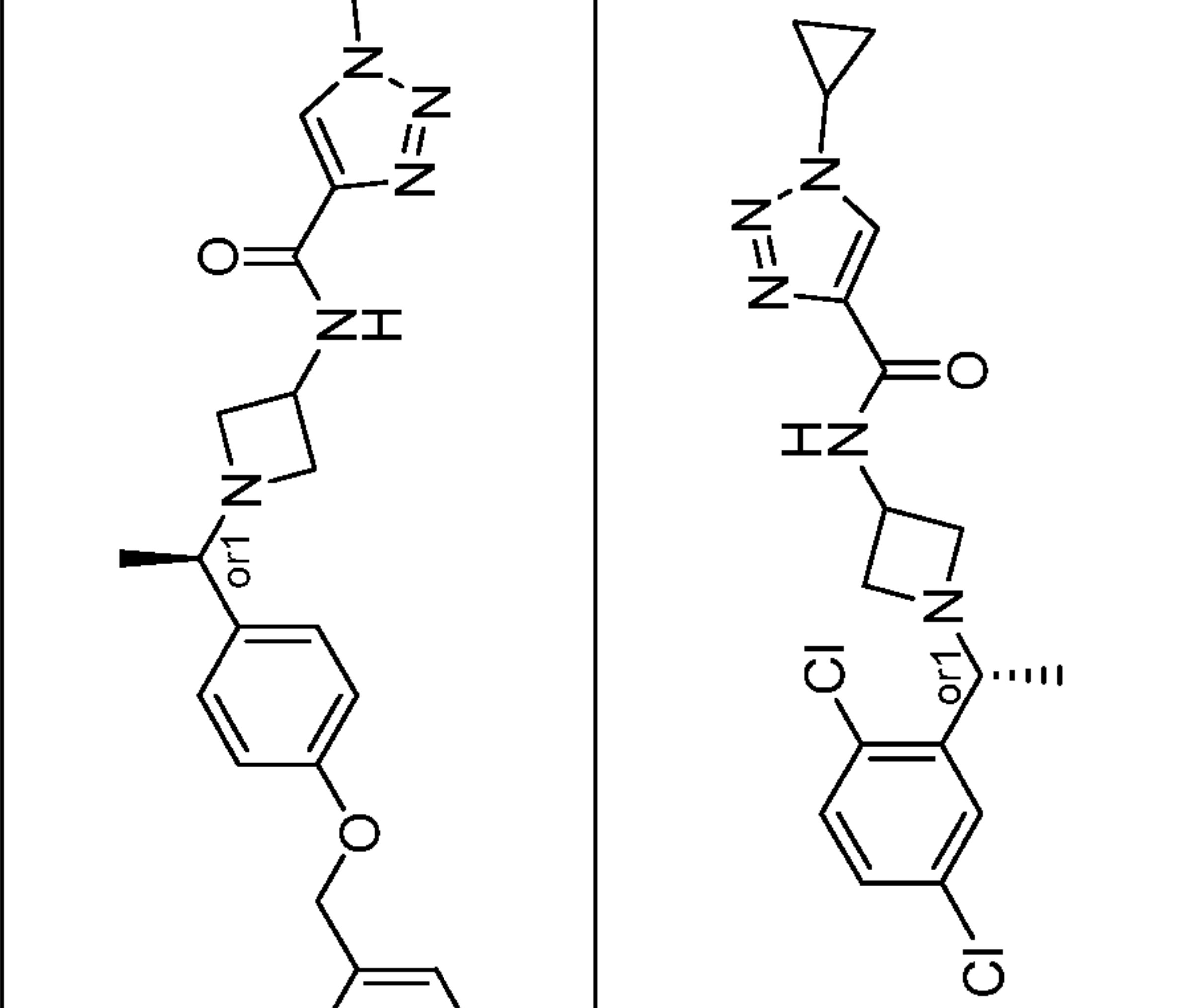
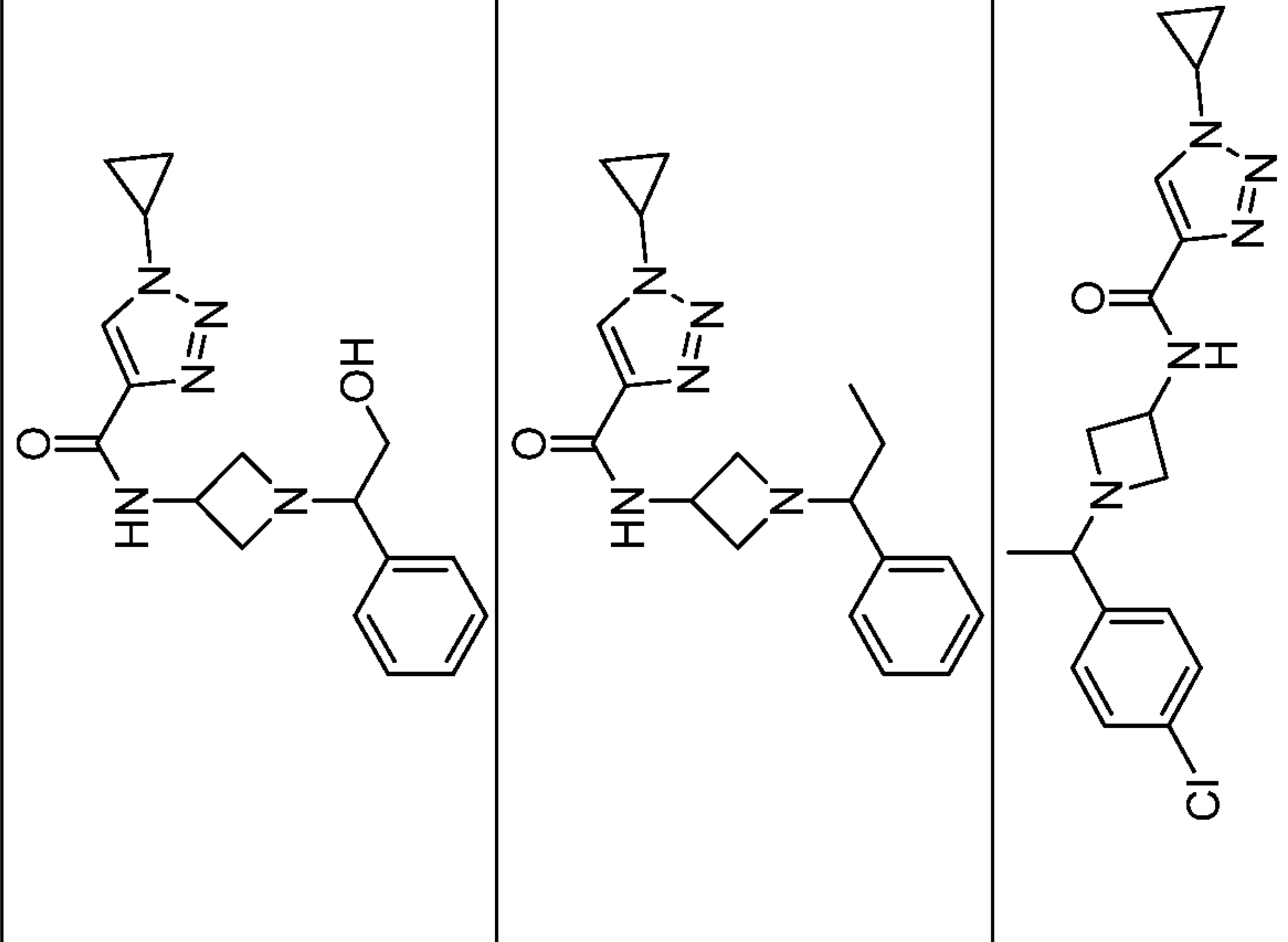
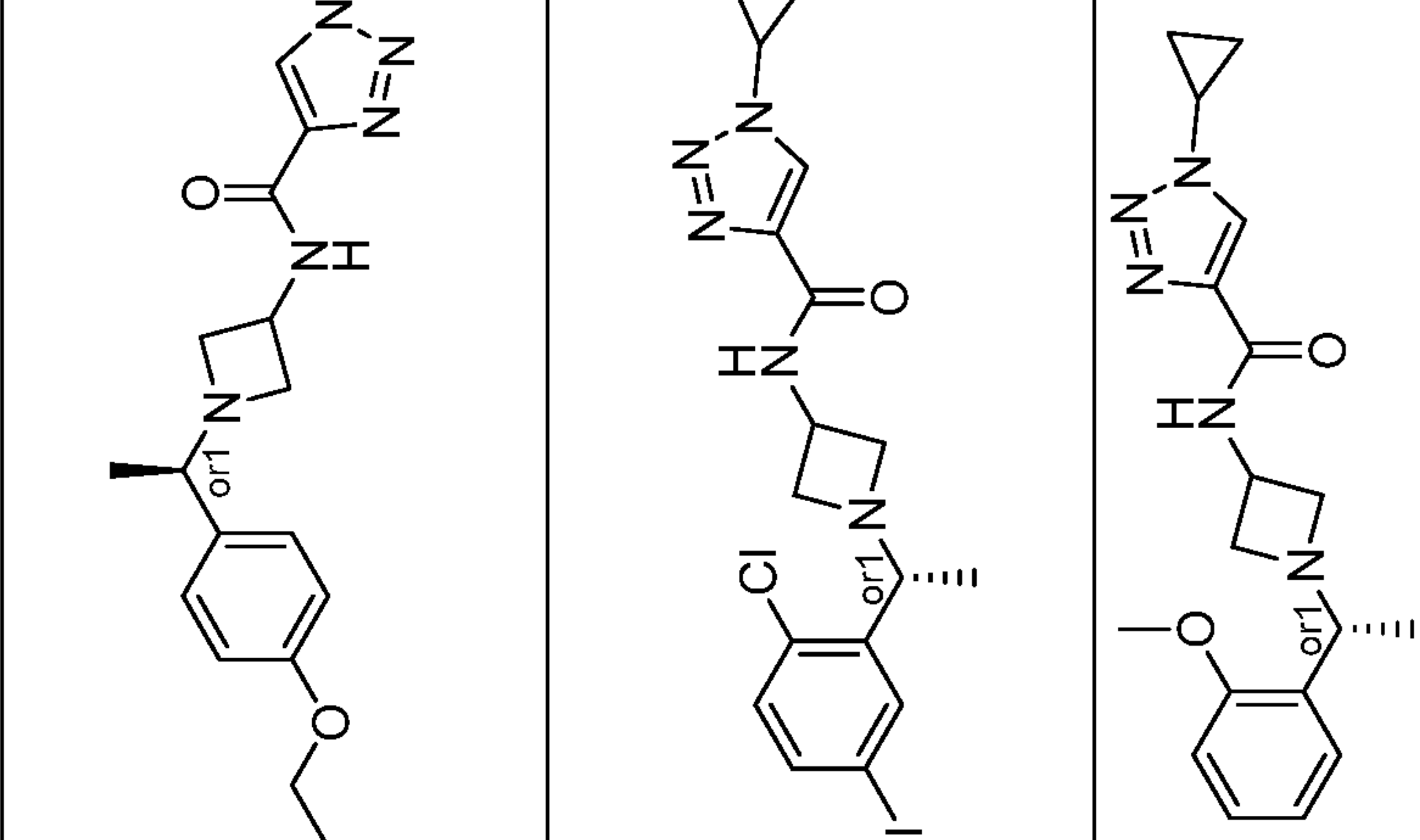
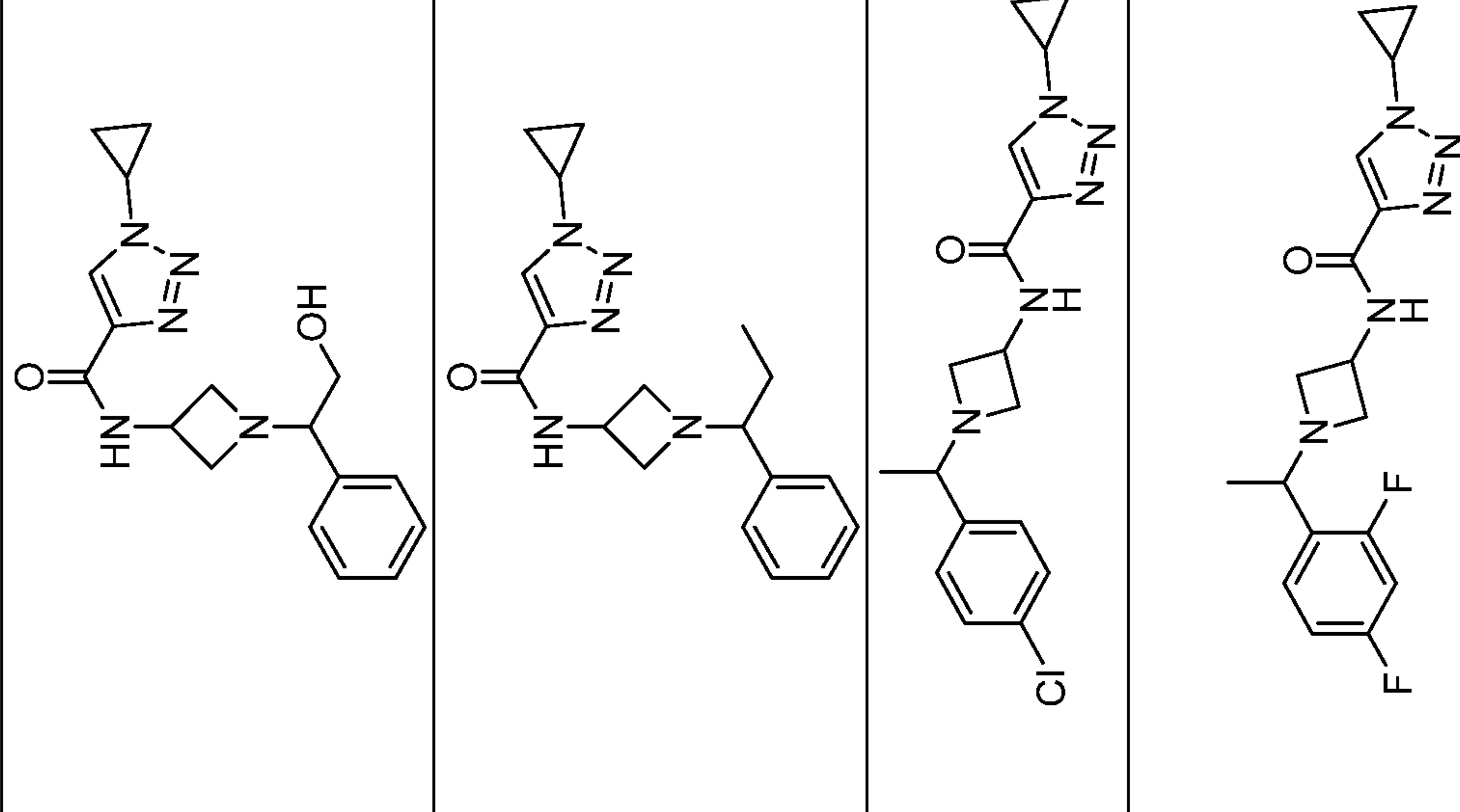
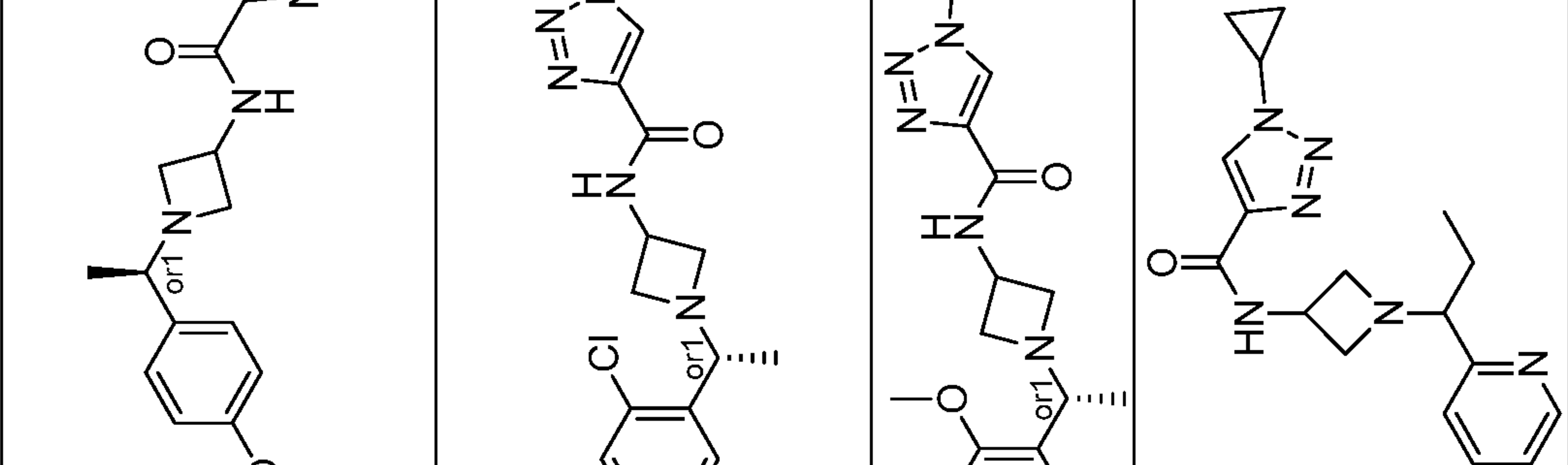
Cpd. No.	Structure	Salt Form	Cpd. No.	Structure	Salt Form
645		None	763		None
646		None	764		None
647		None	765		None
648		None	766		None

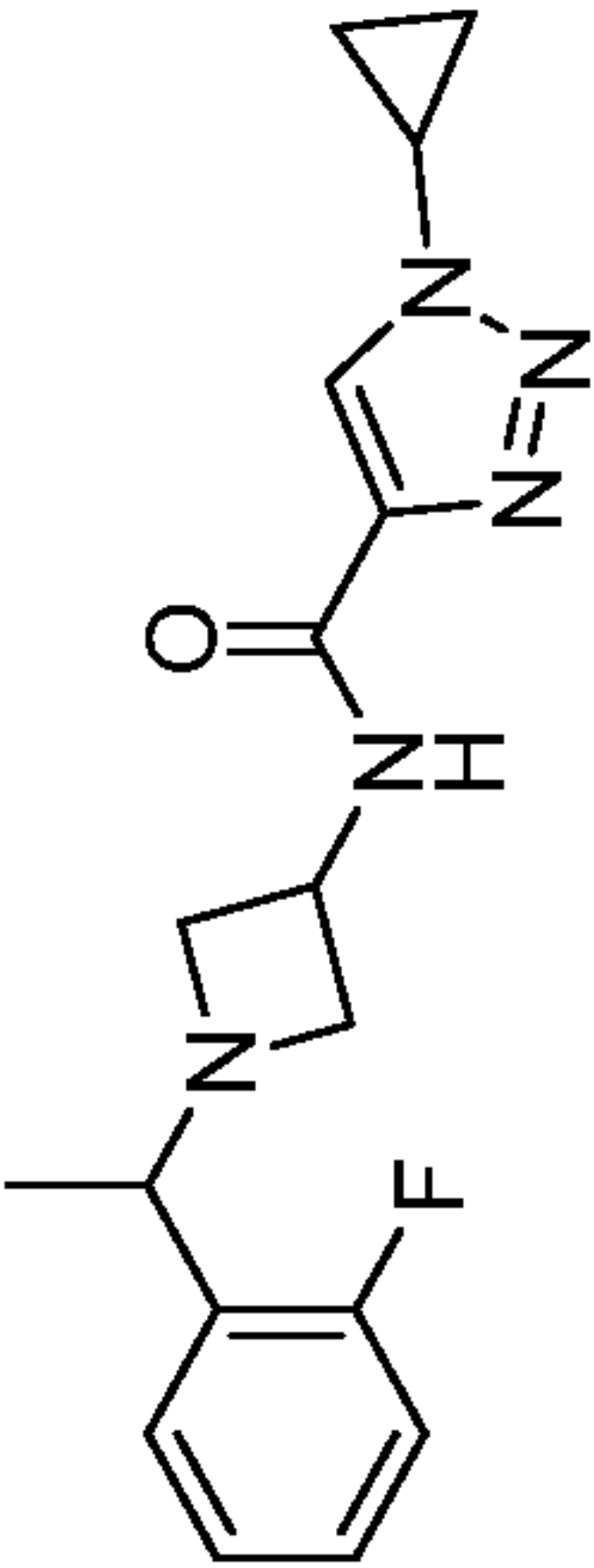
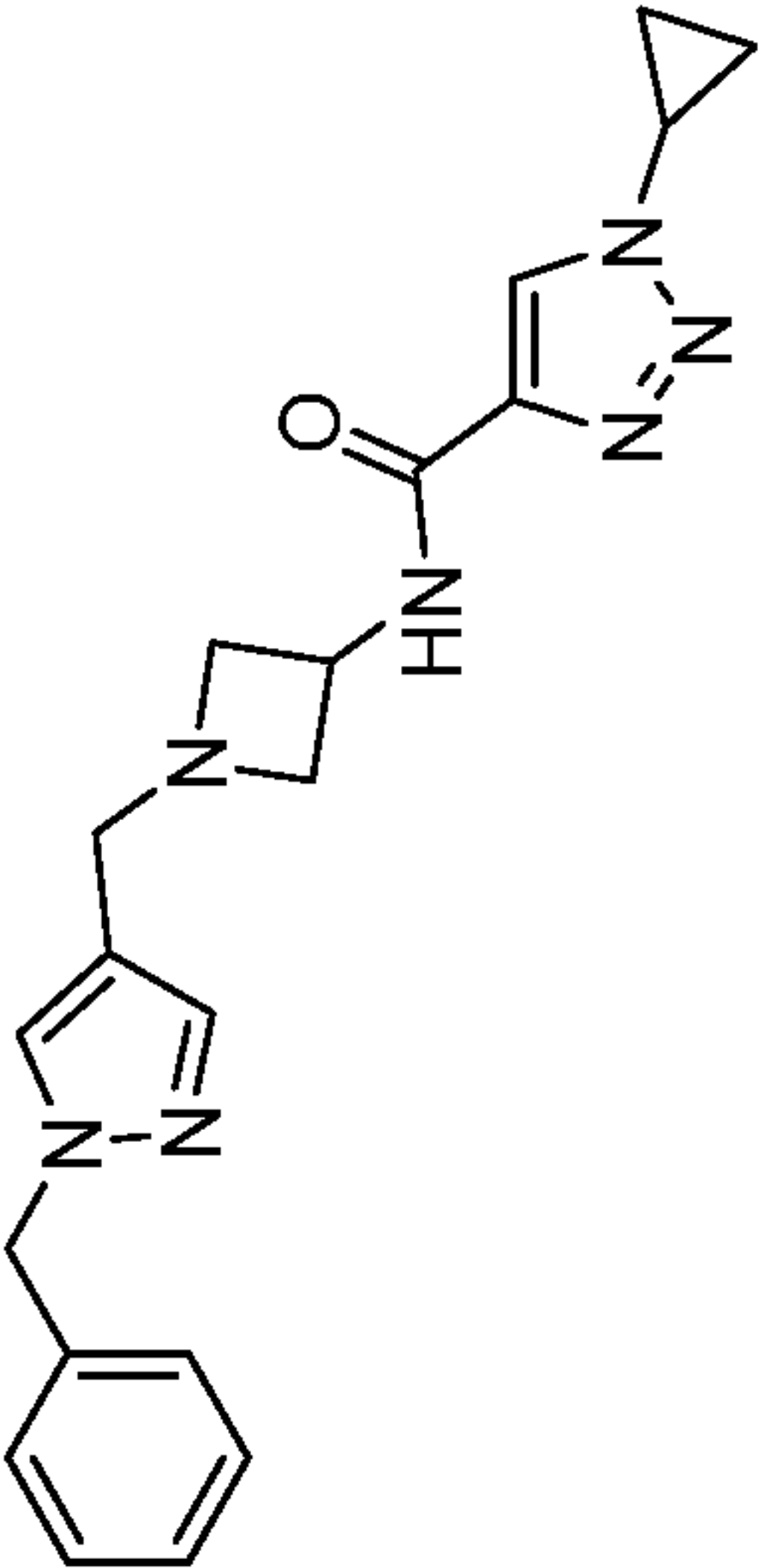
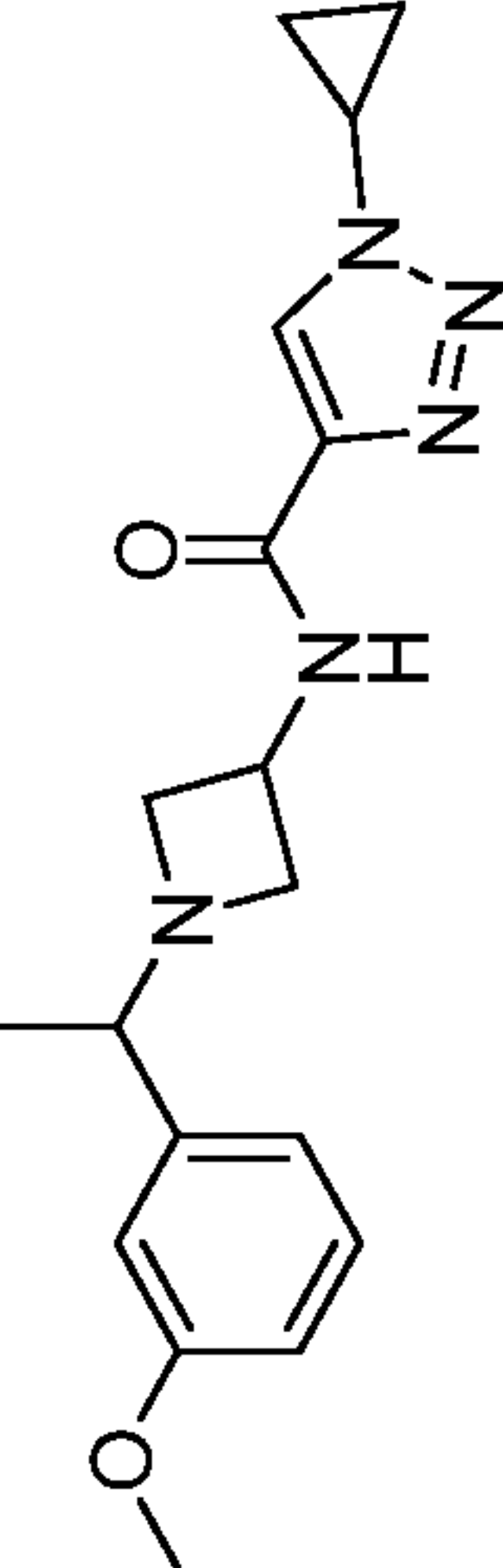
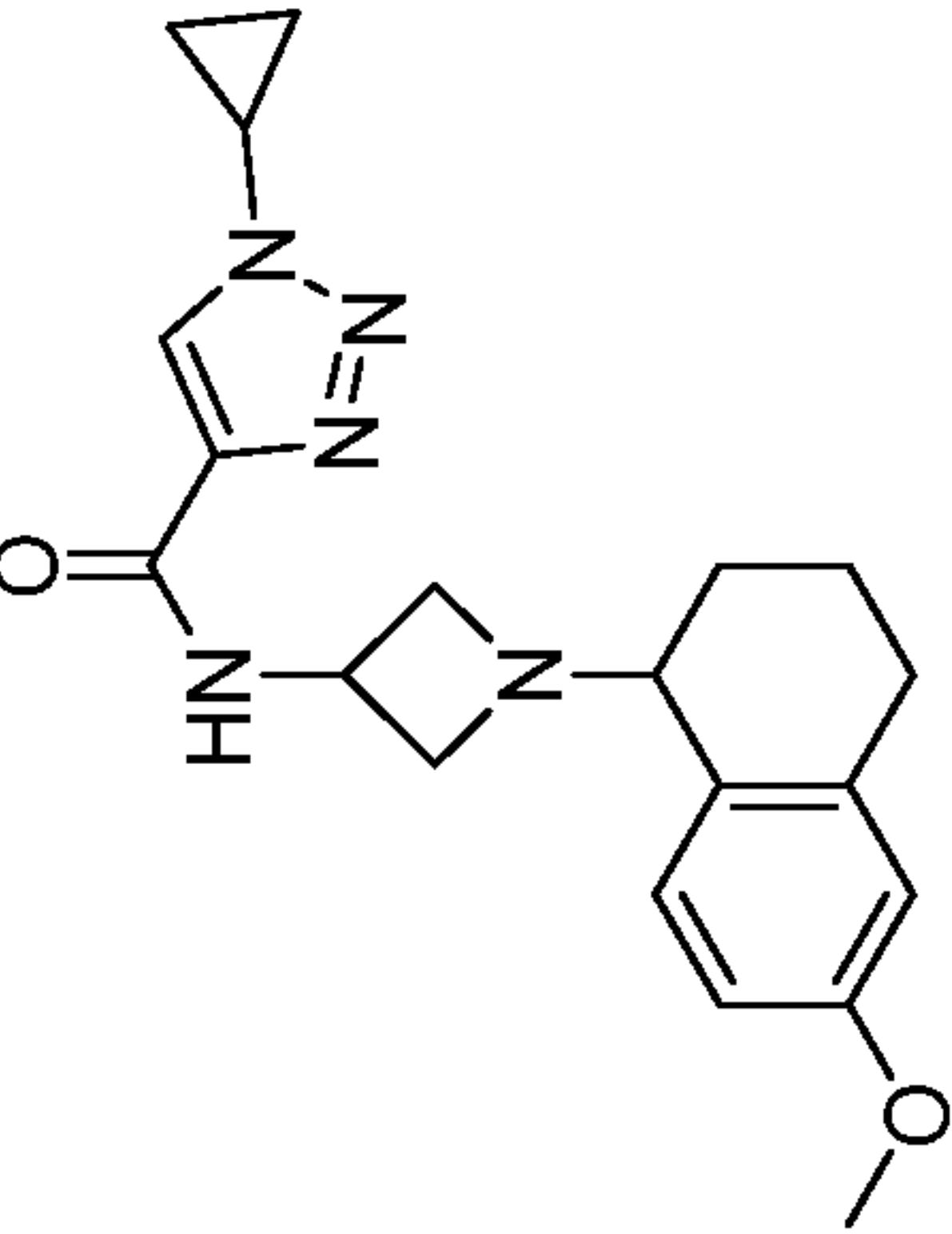
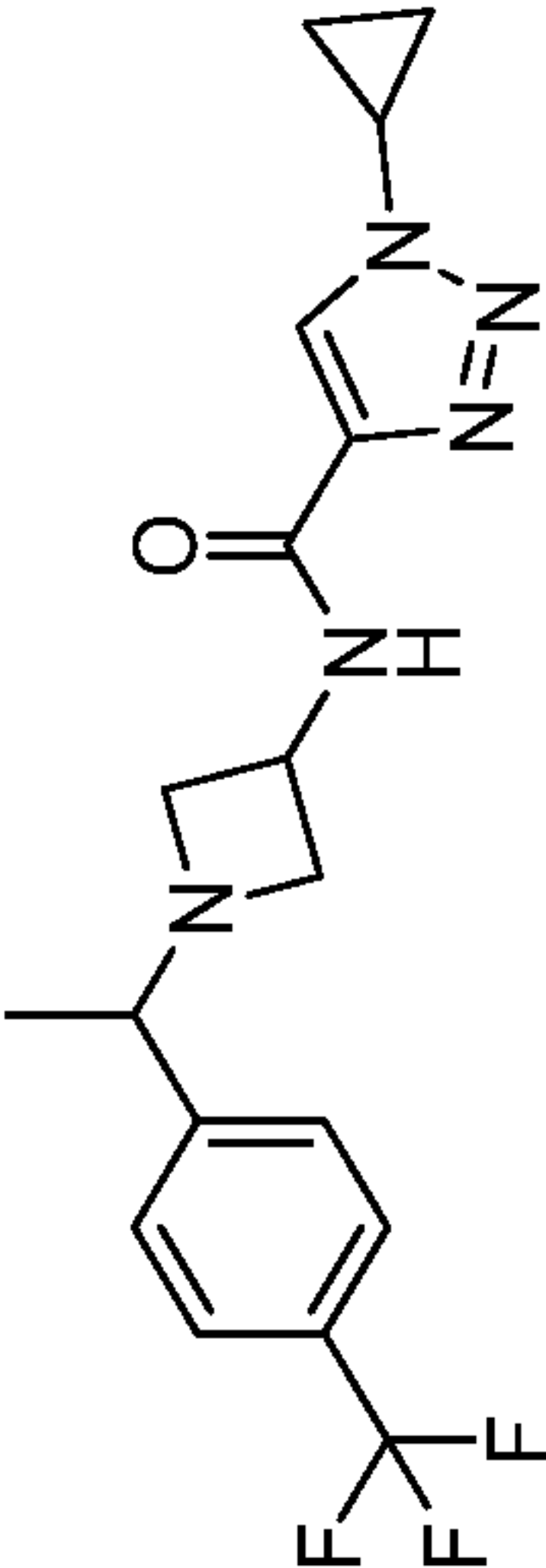
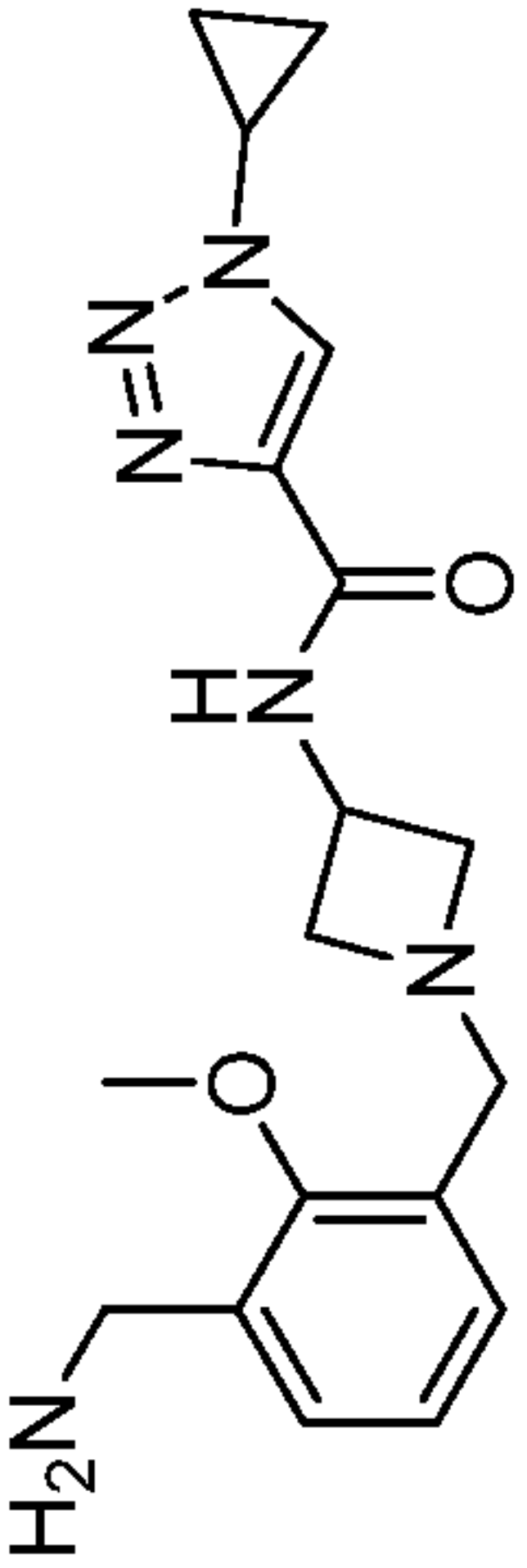
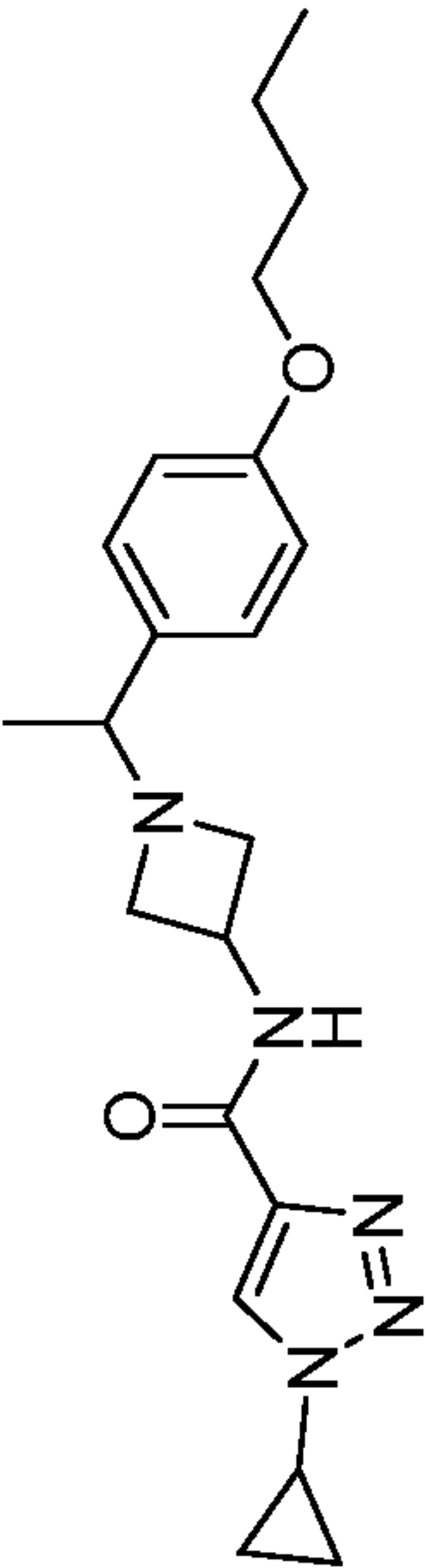
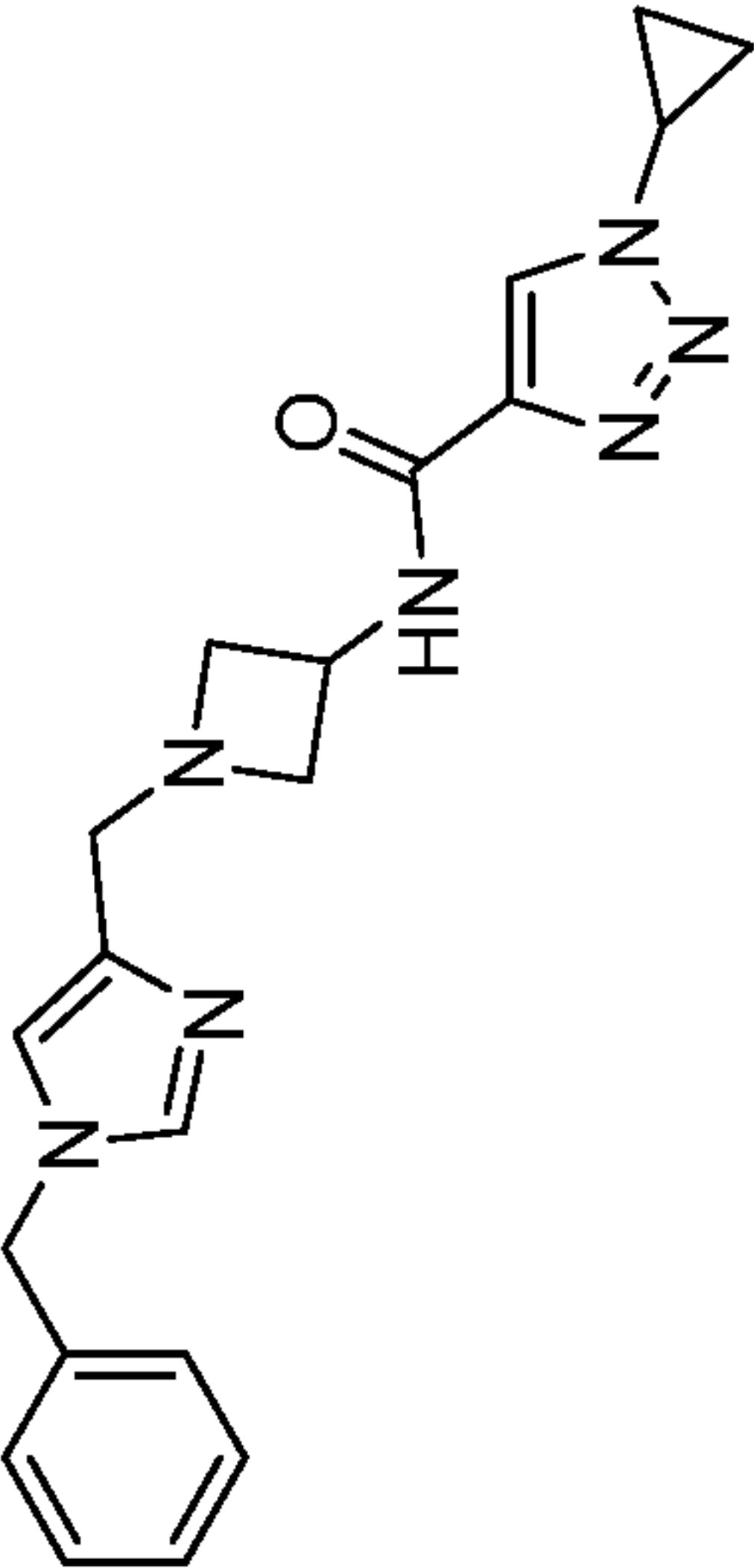
649		None	767		None
650		None	768		None
651		None	769		None
652		None	770		None
657		None	771		None
			772		None

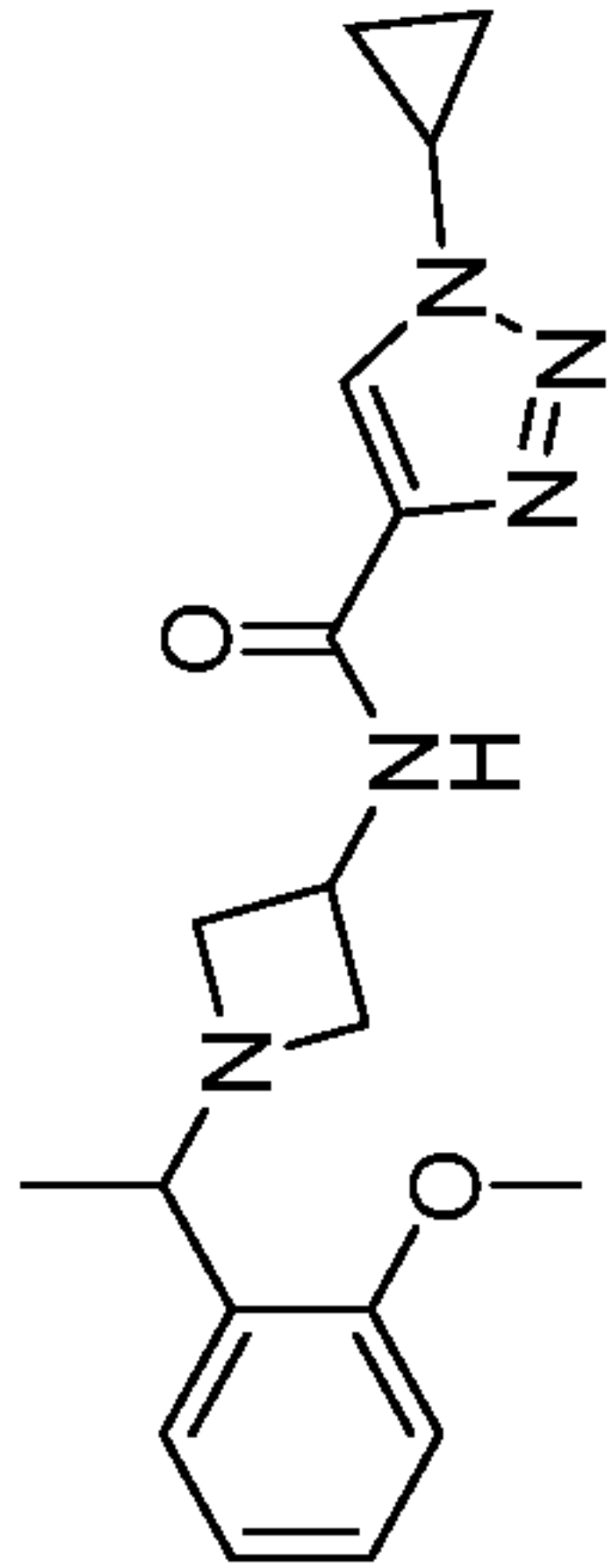
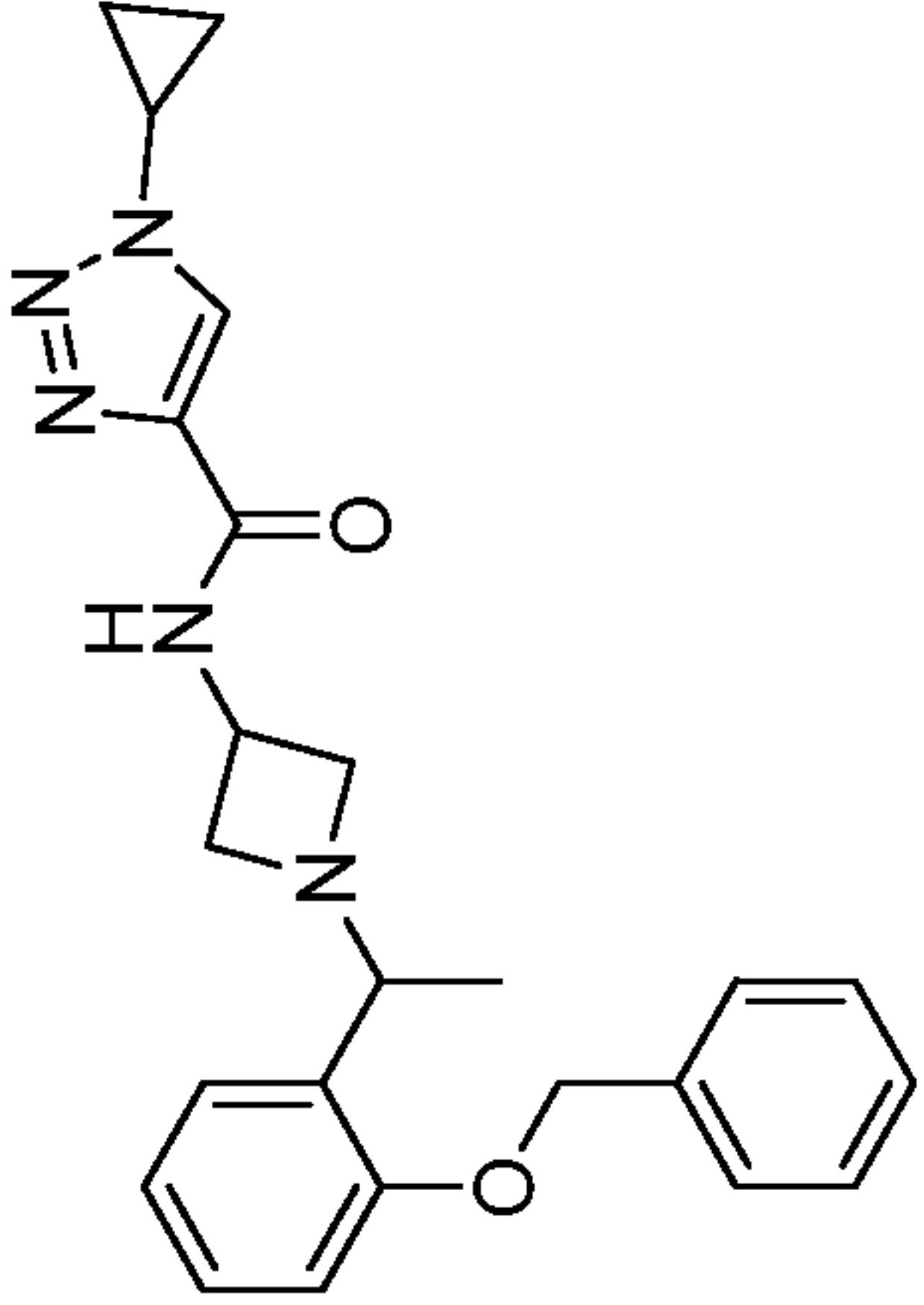
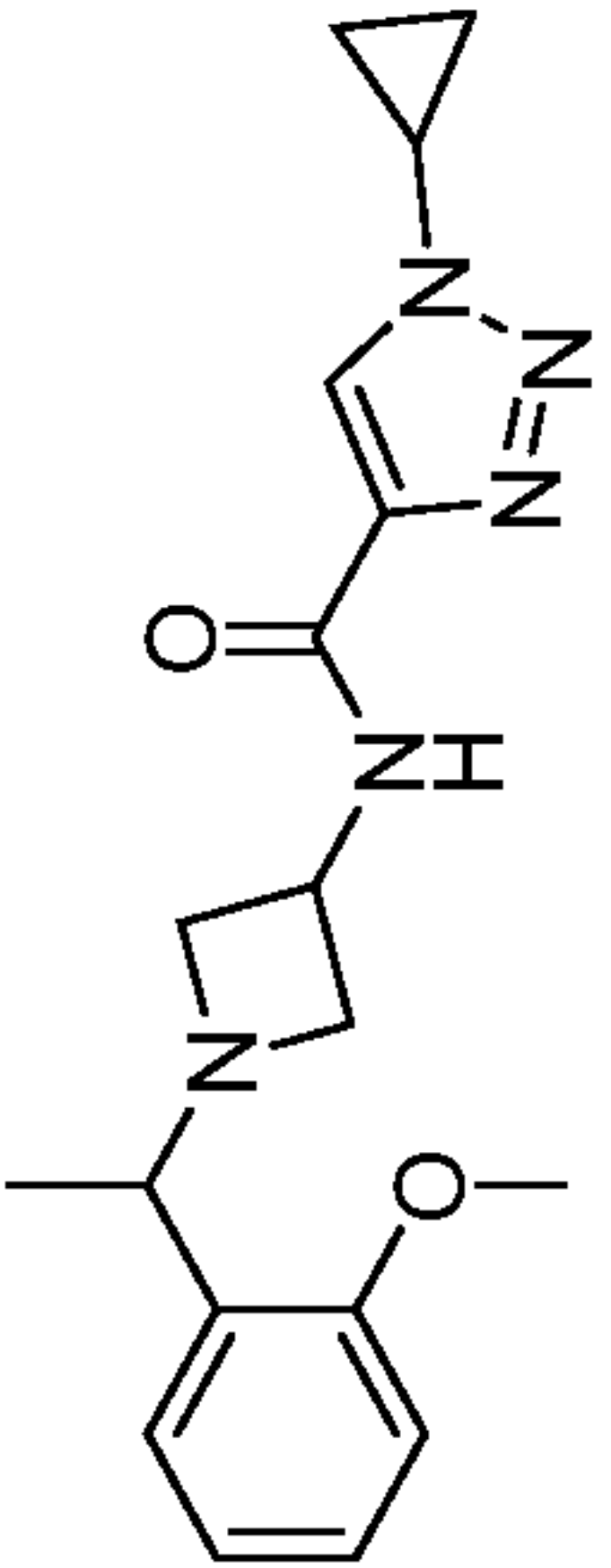
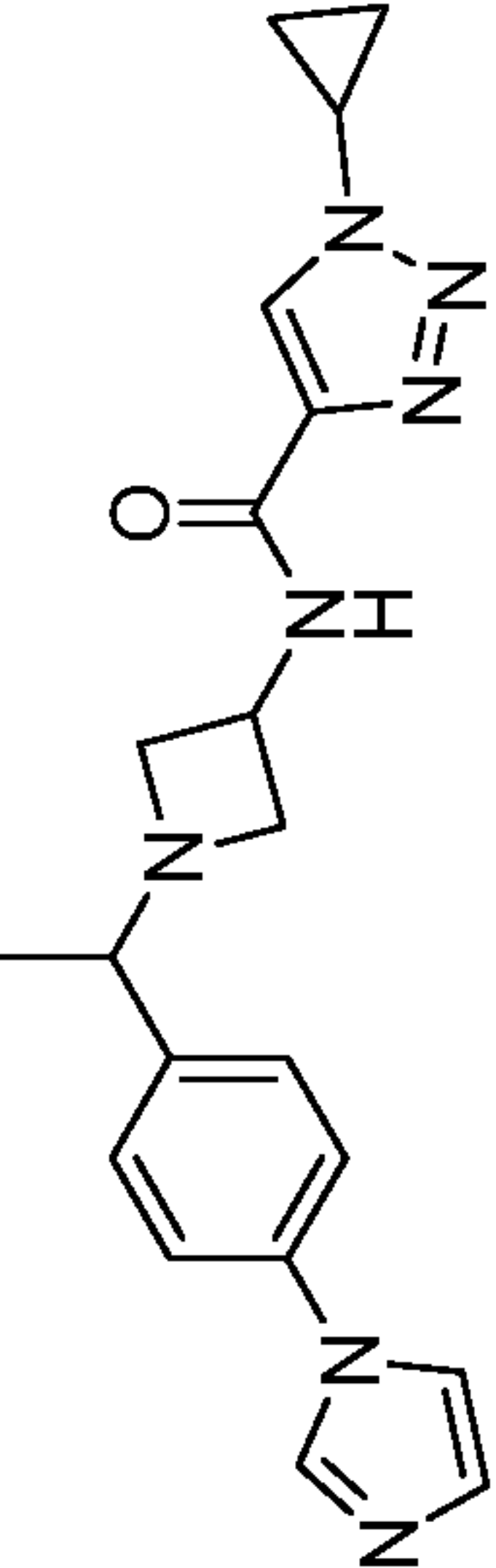
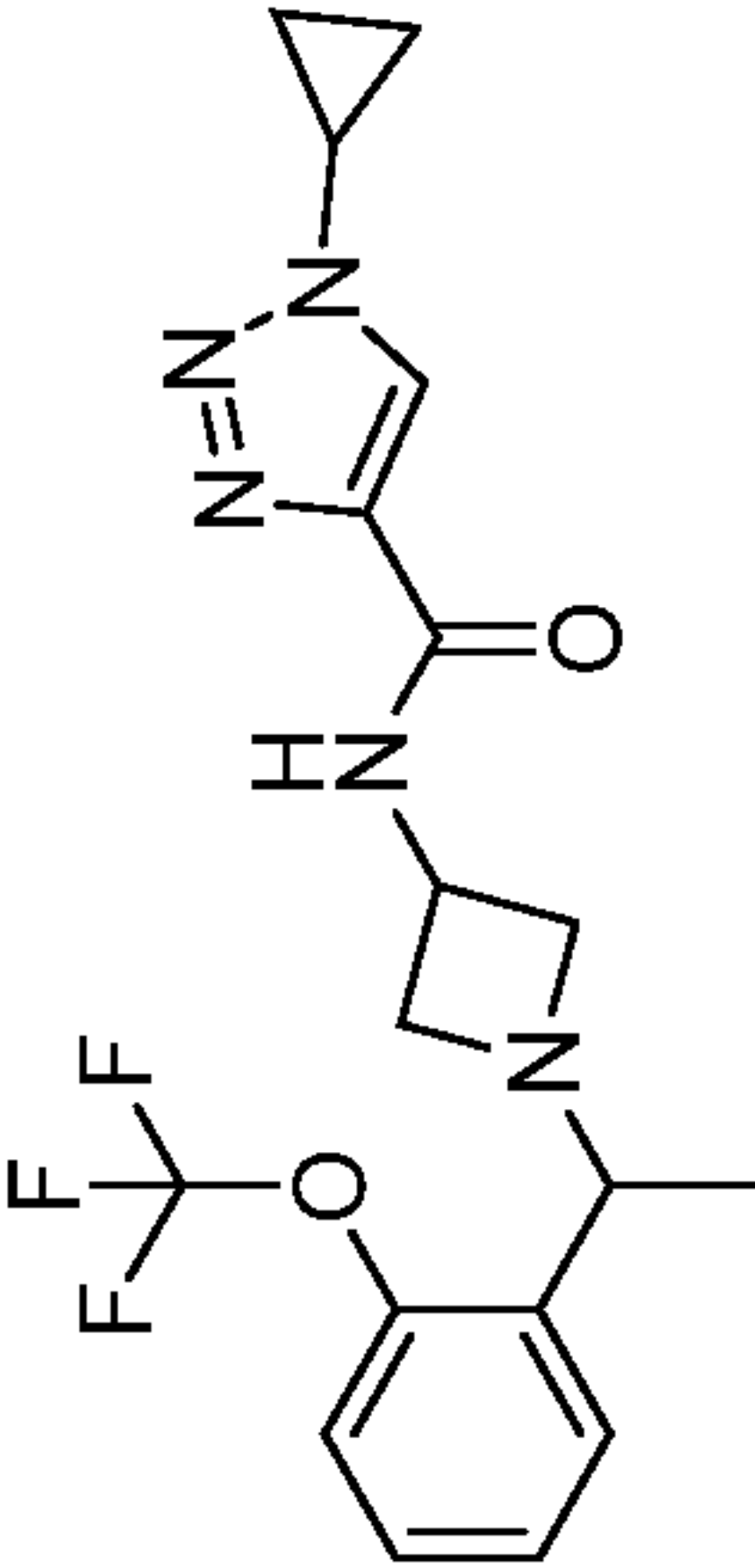
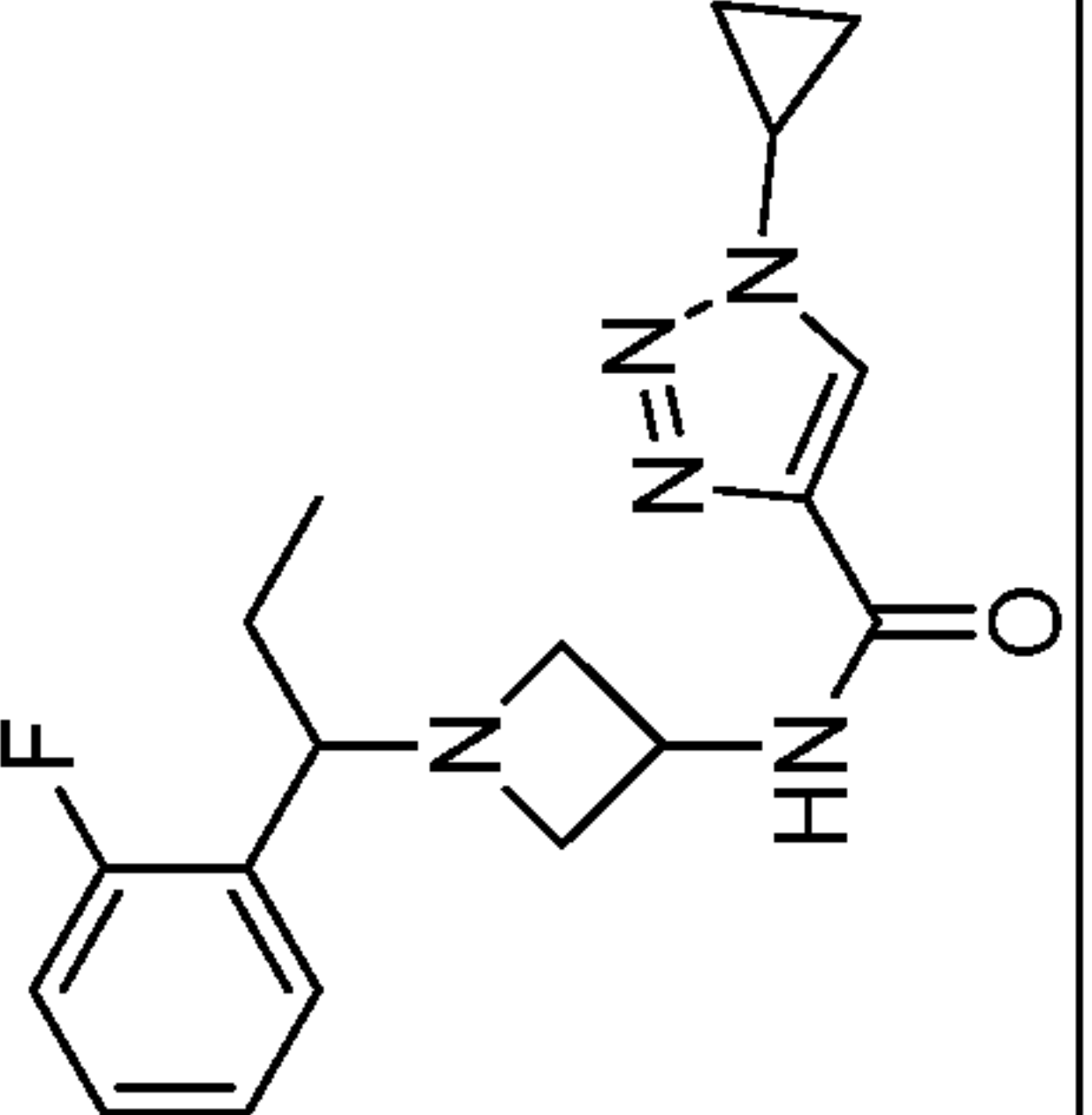
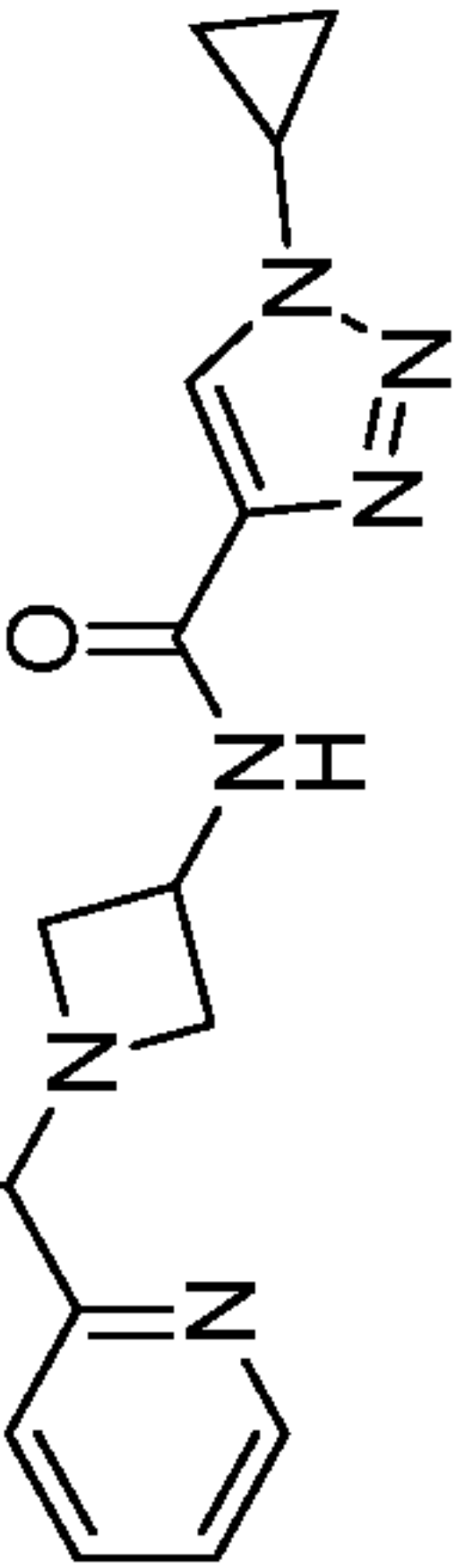
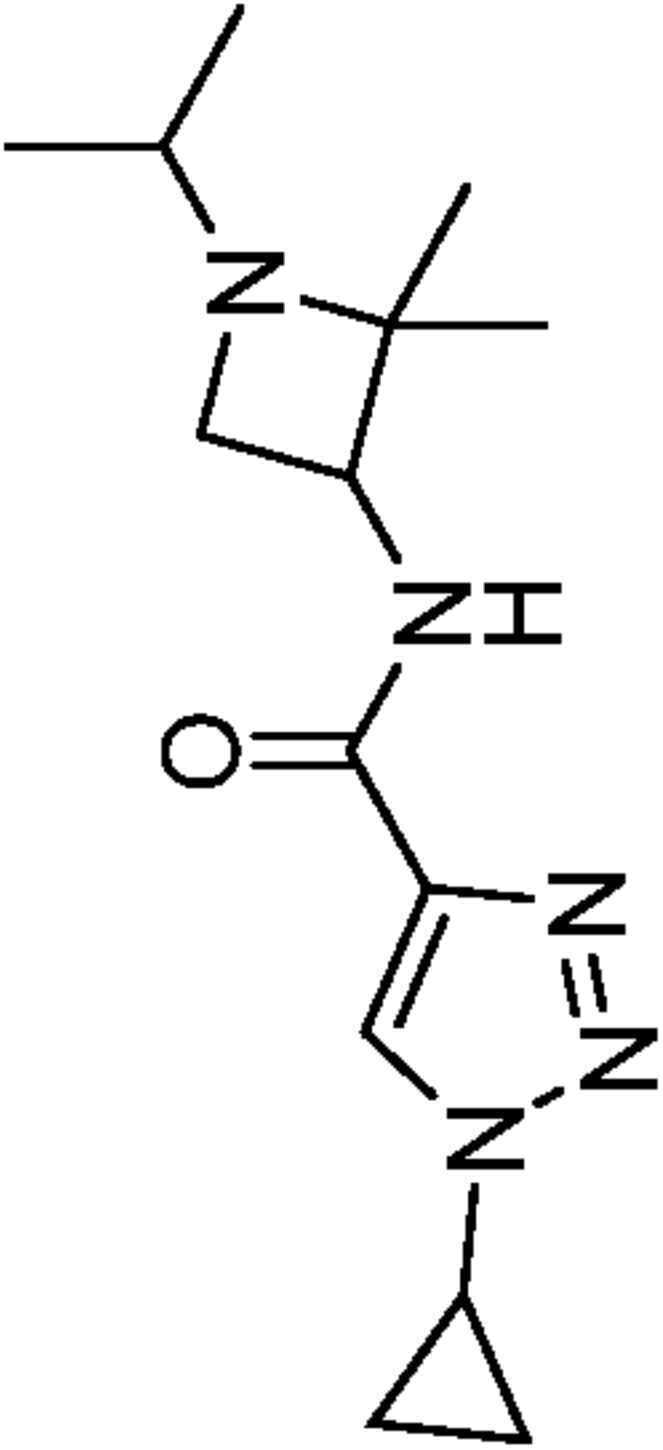
659		None	773		None
660		None	774		None
661		None	775		None
662		None	776		None
663		None	777		None

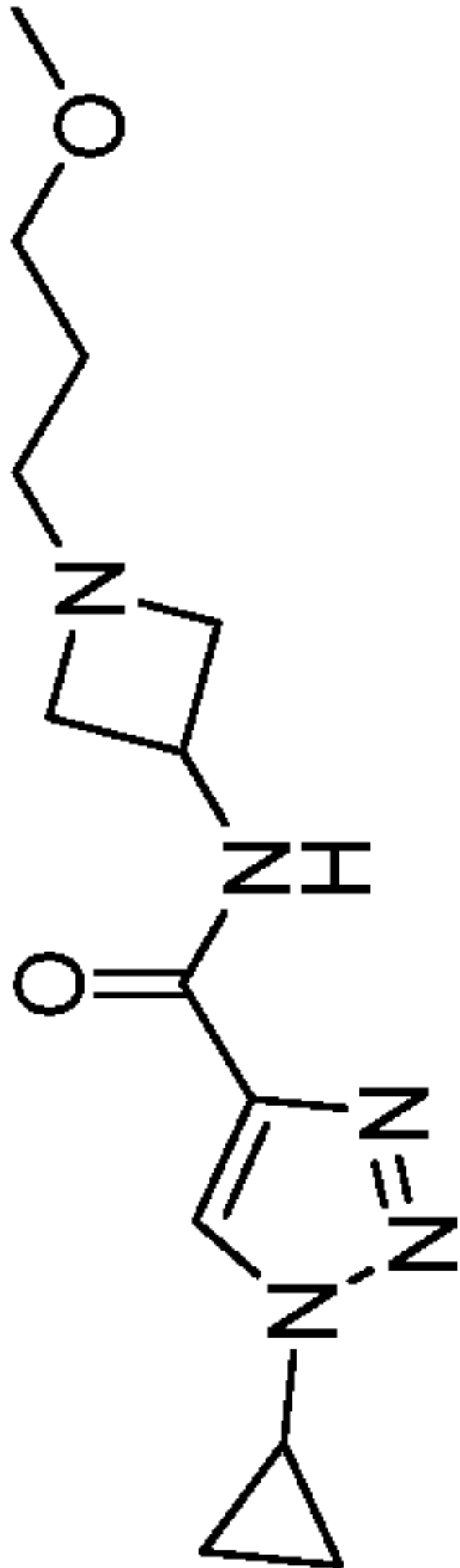
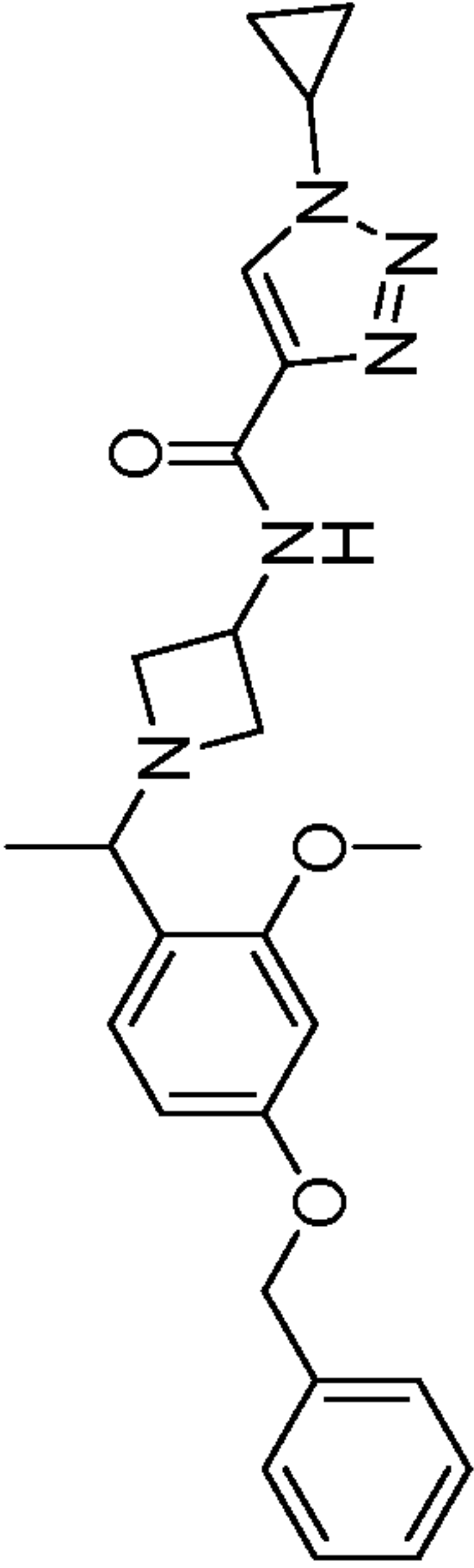
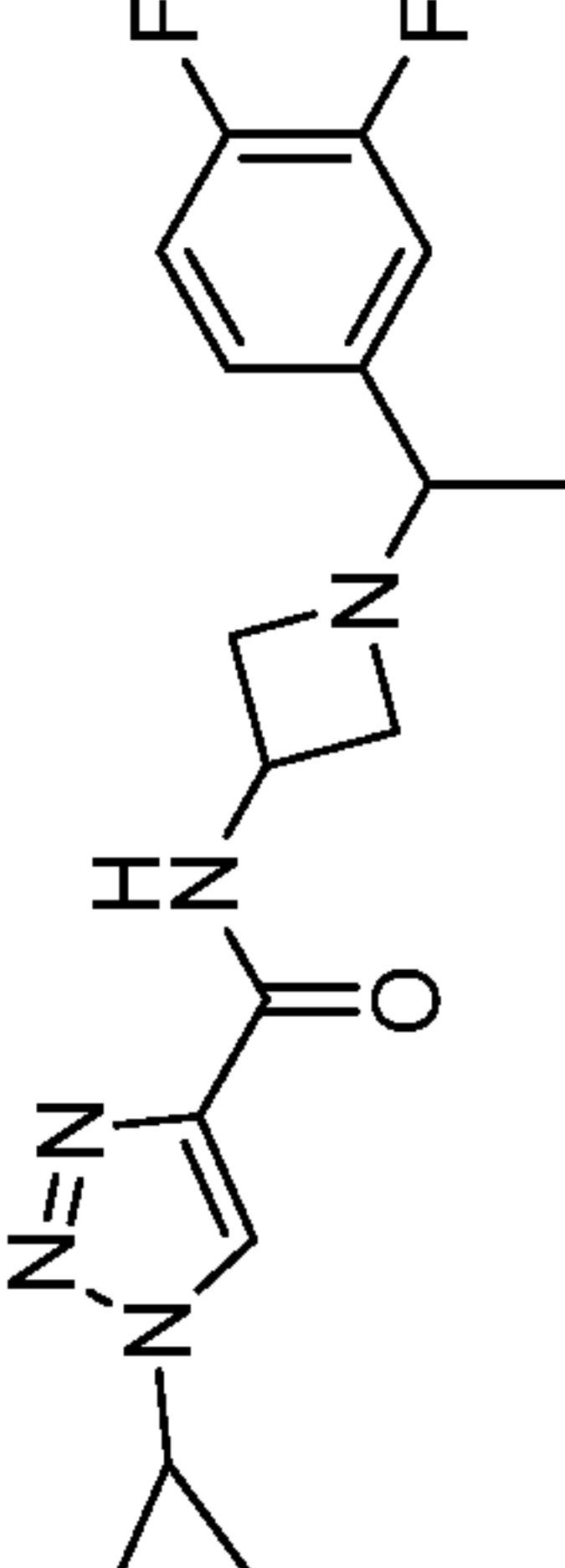
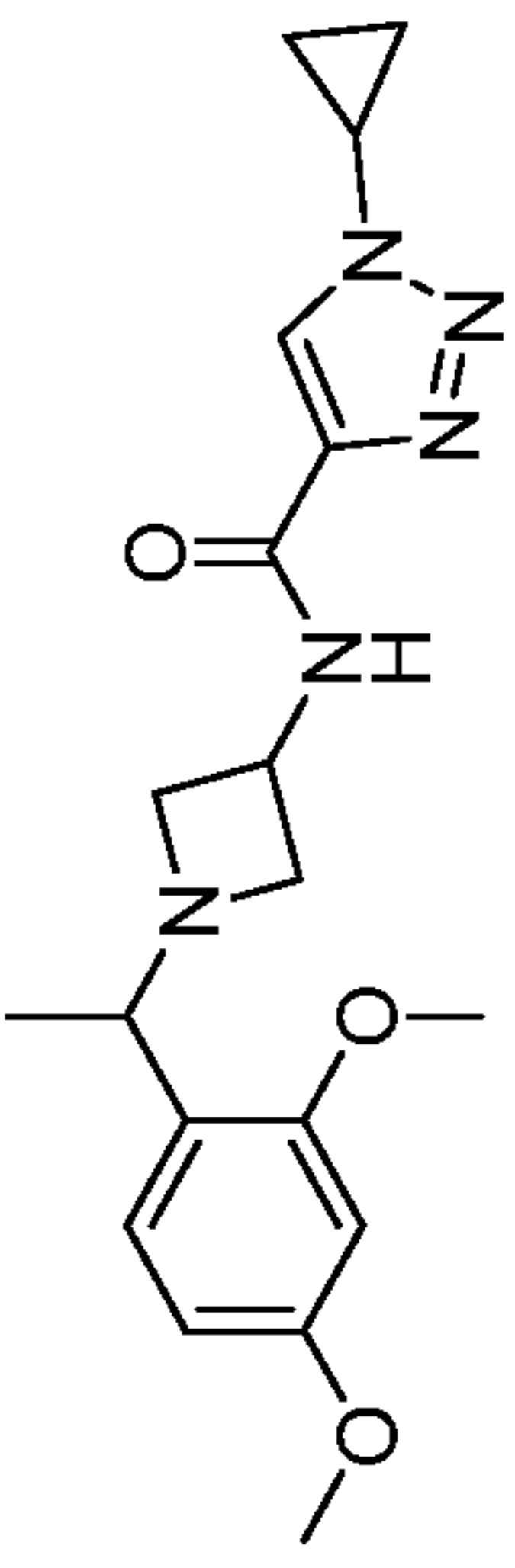
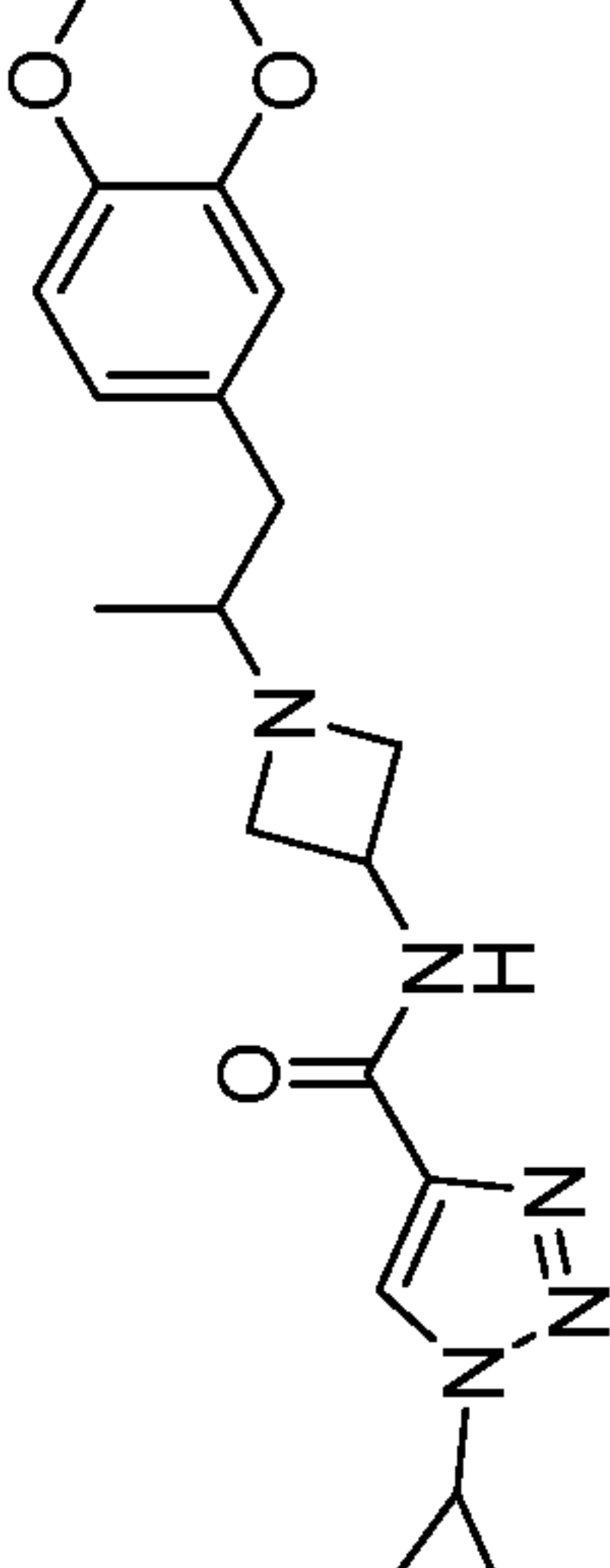
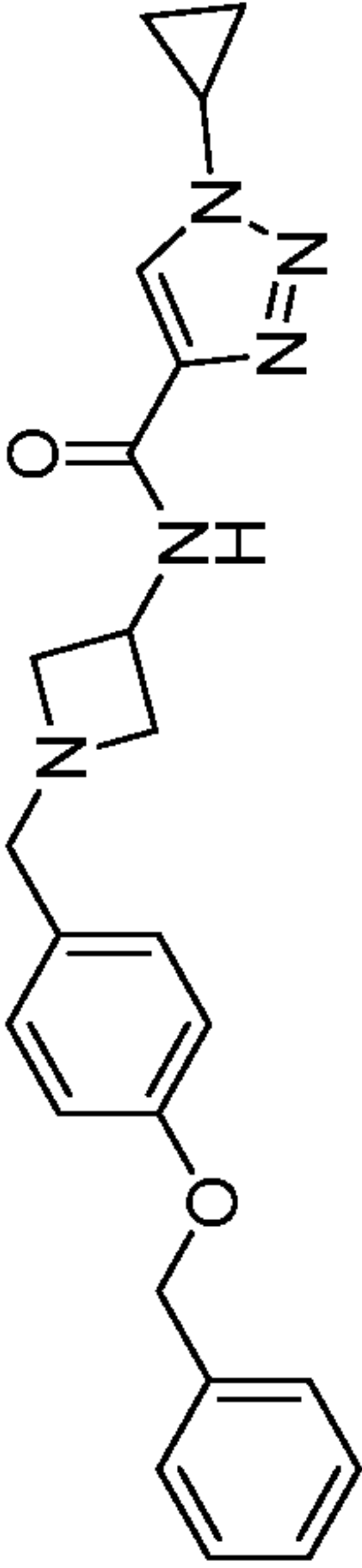
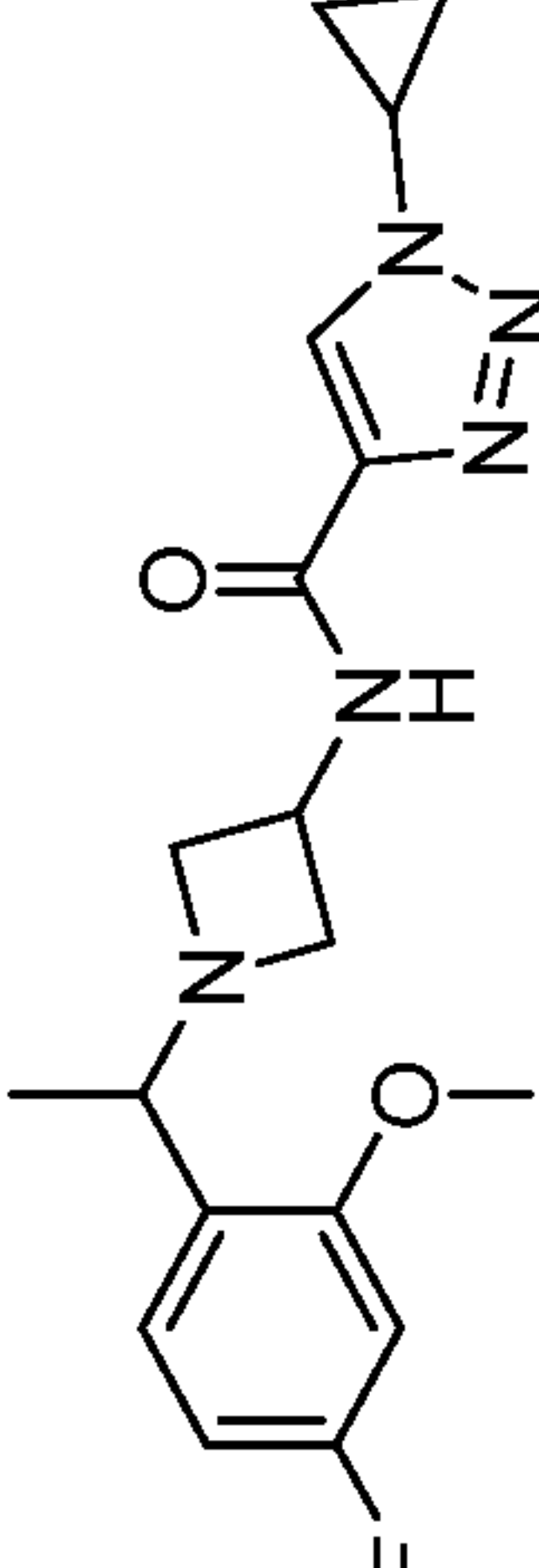
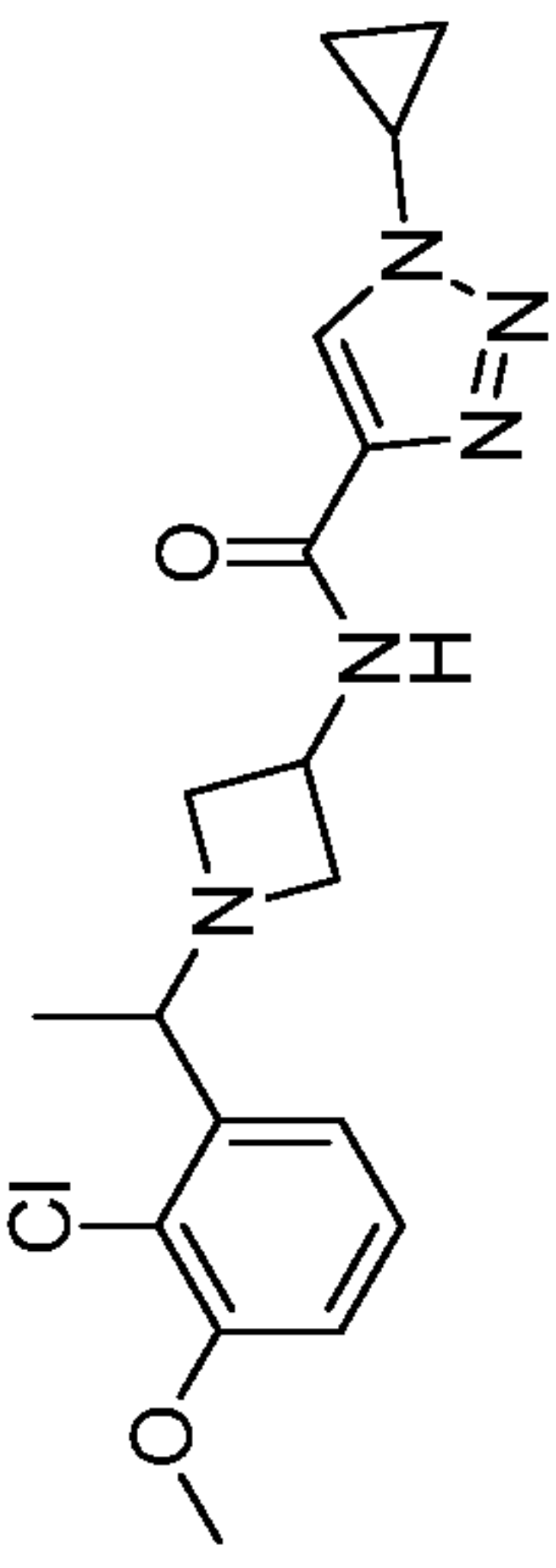
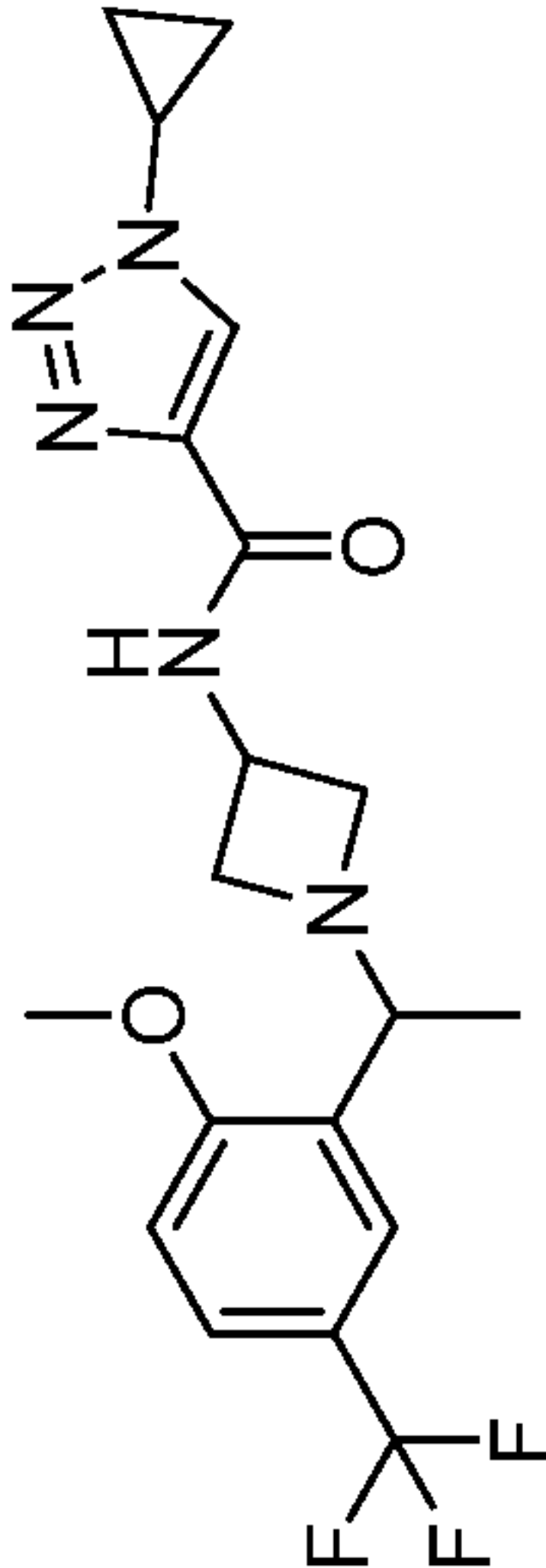
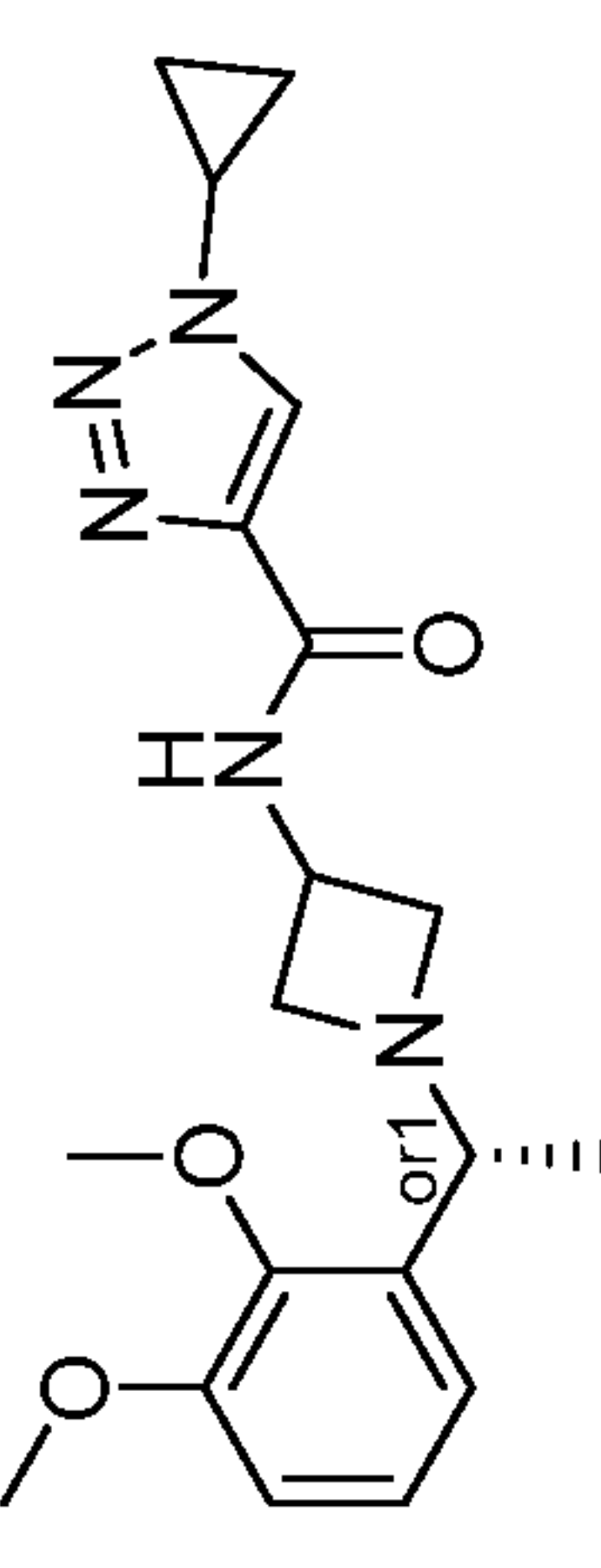
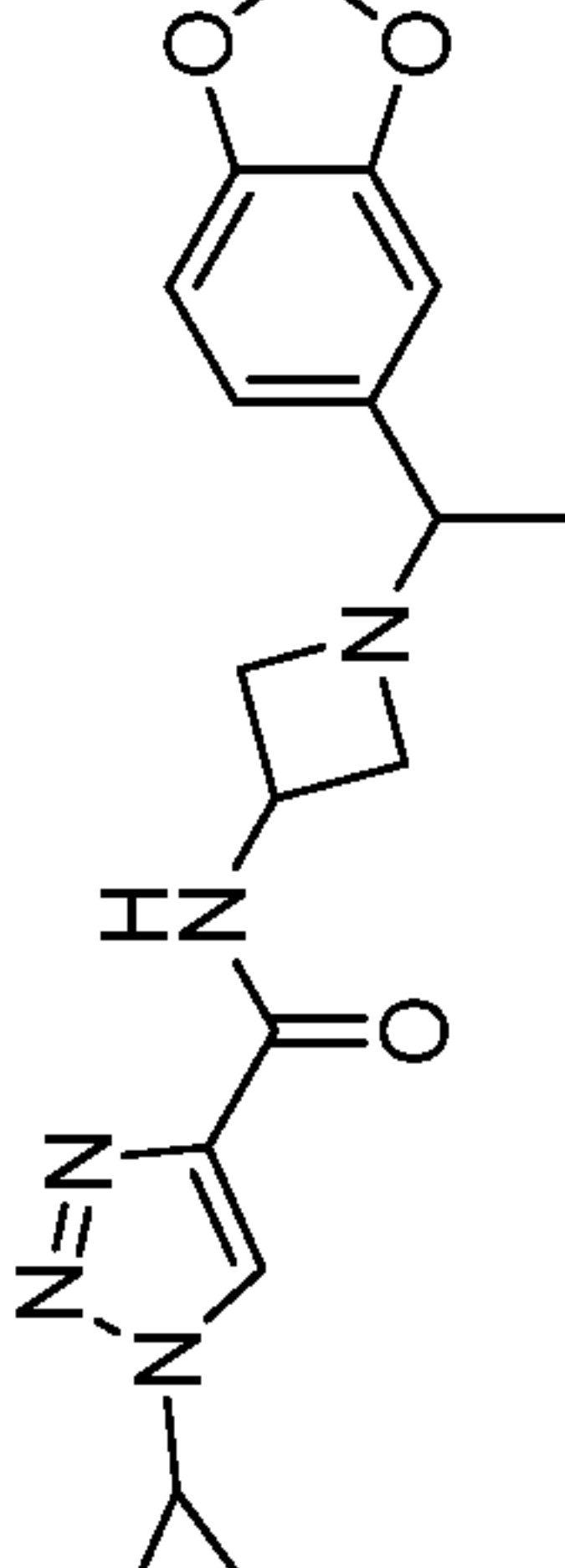
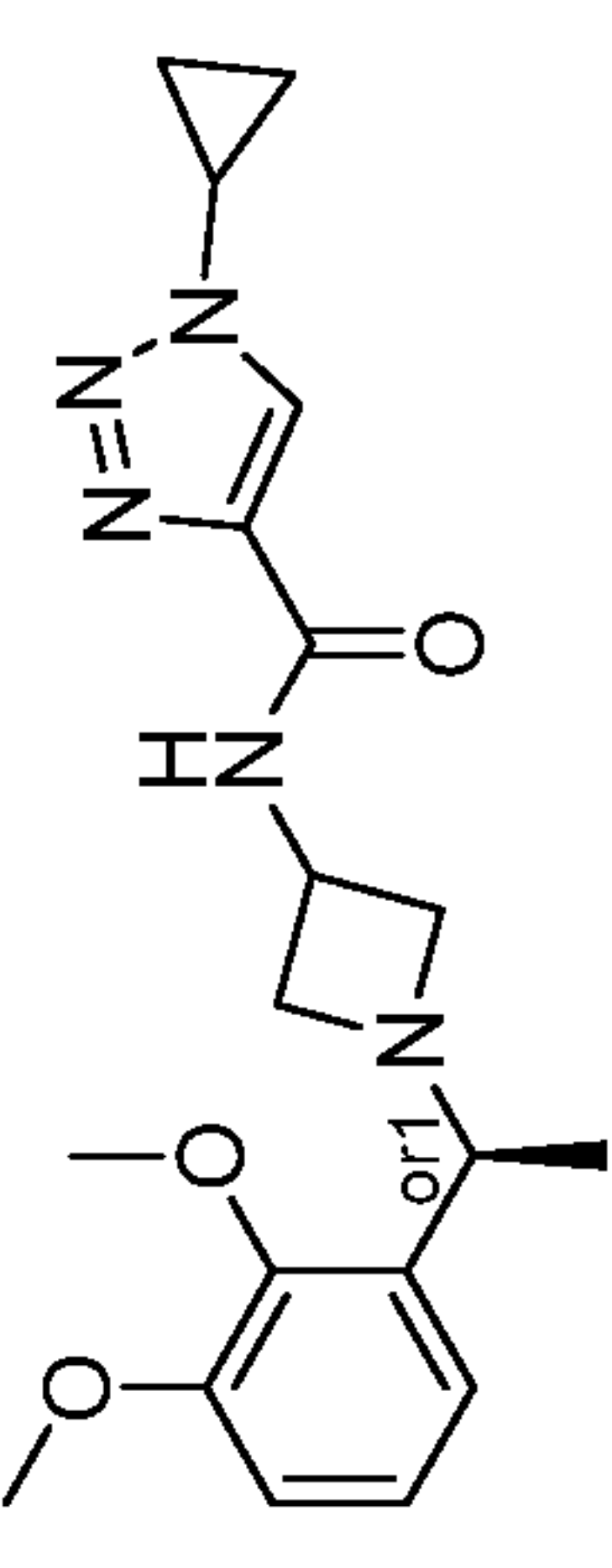
664		None	778		None
665		None	779		None
666		None	780		None
667		None	781		None
668		None	782		None

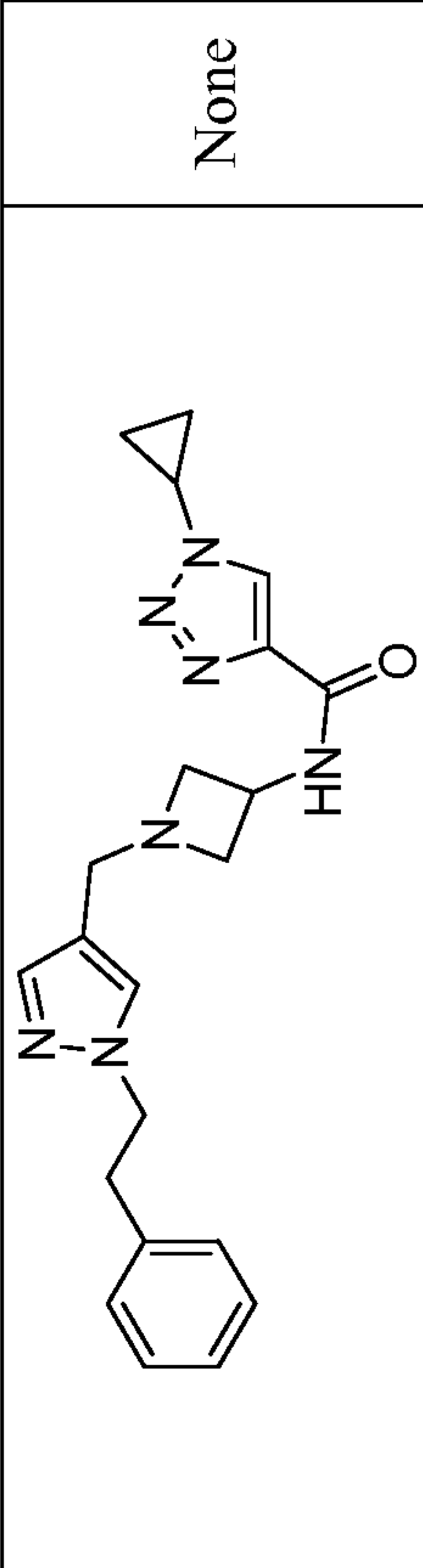
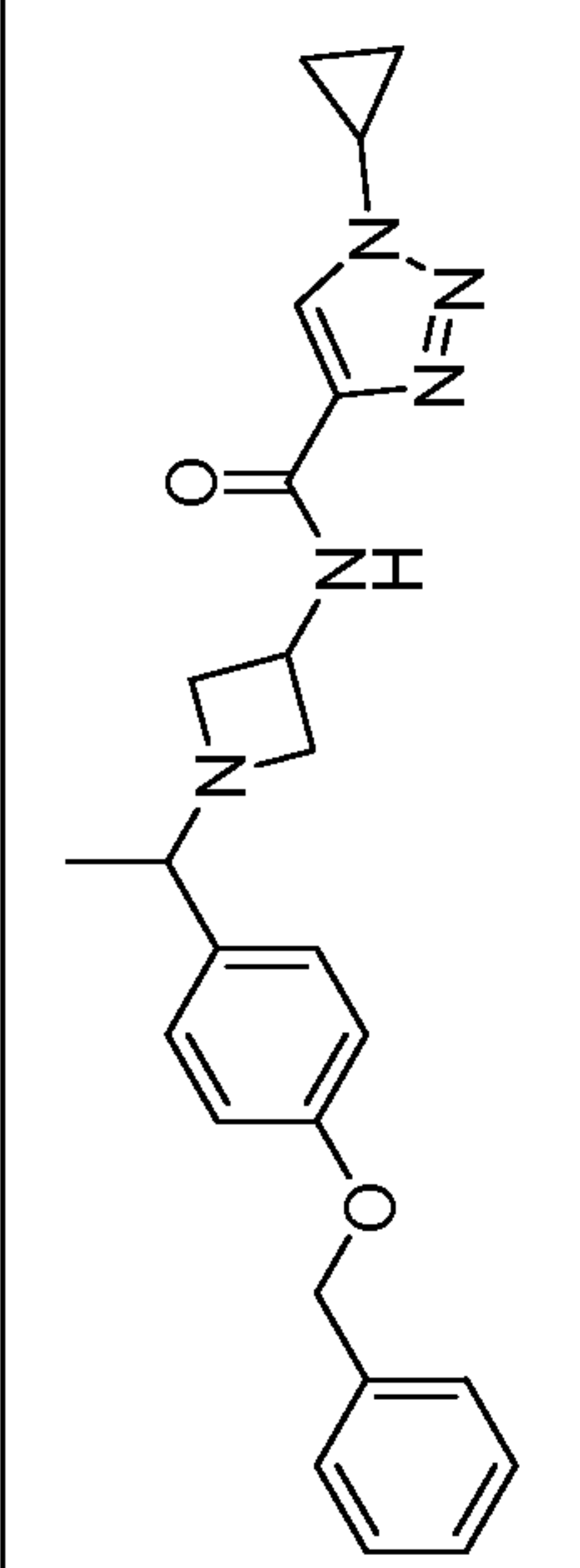
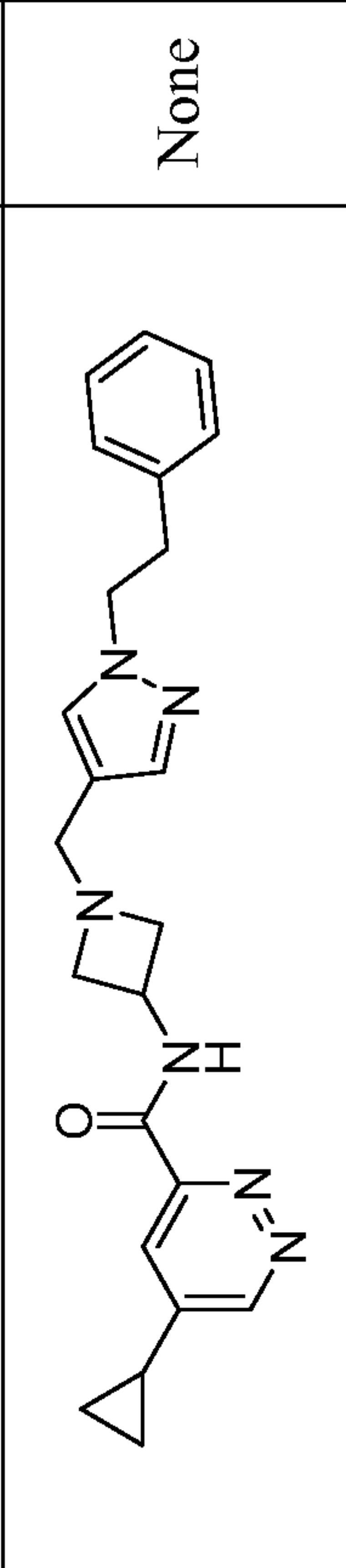
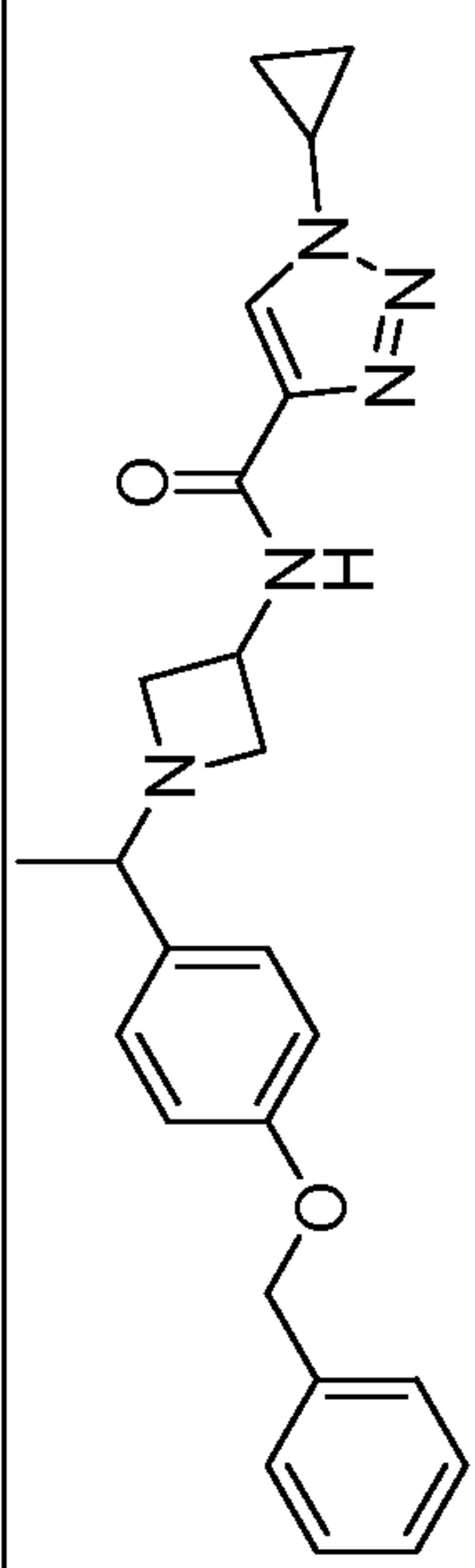
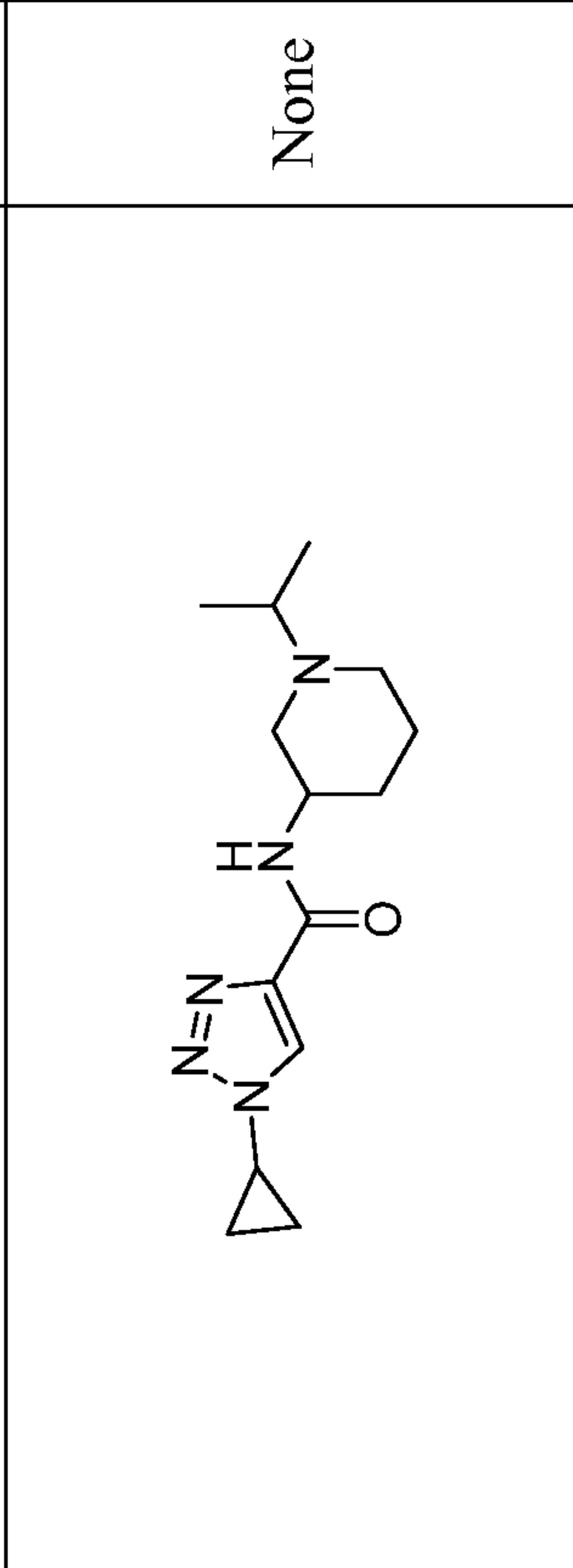
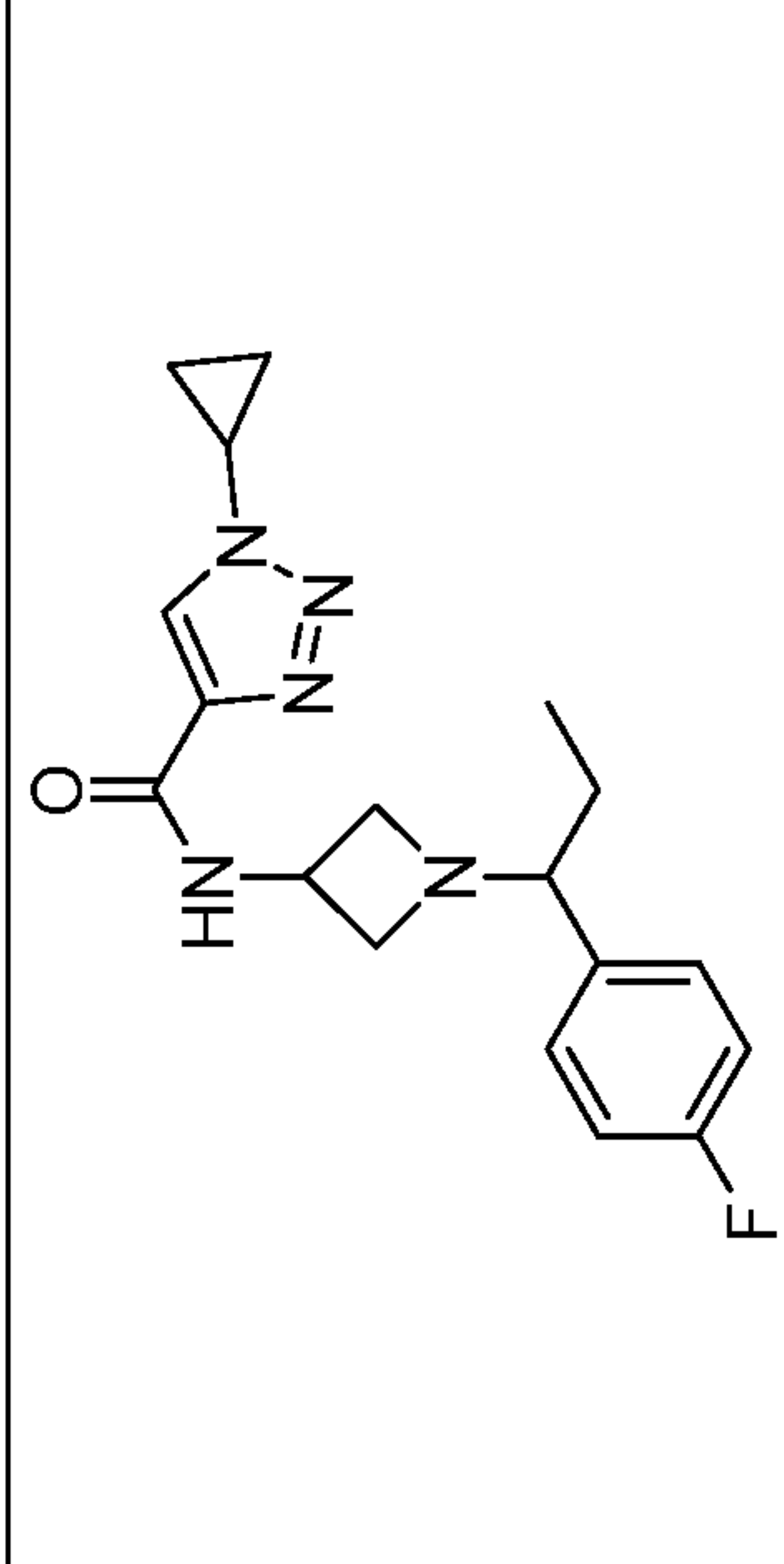
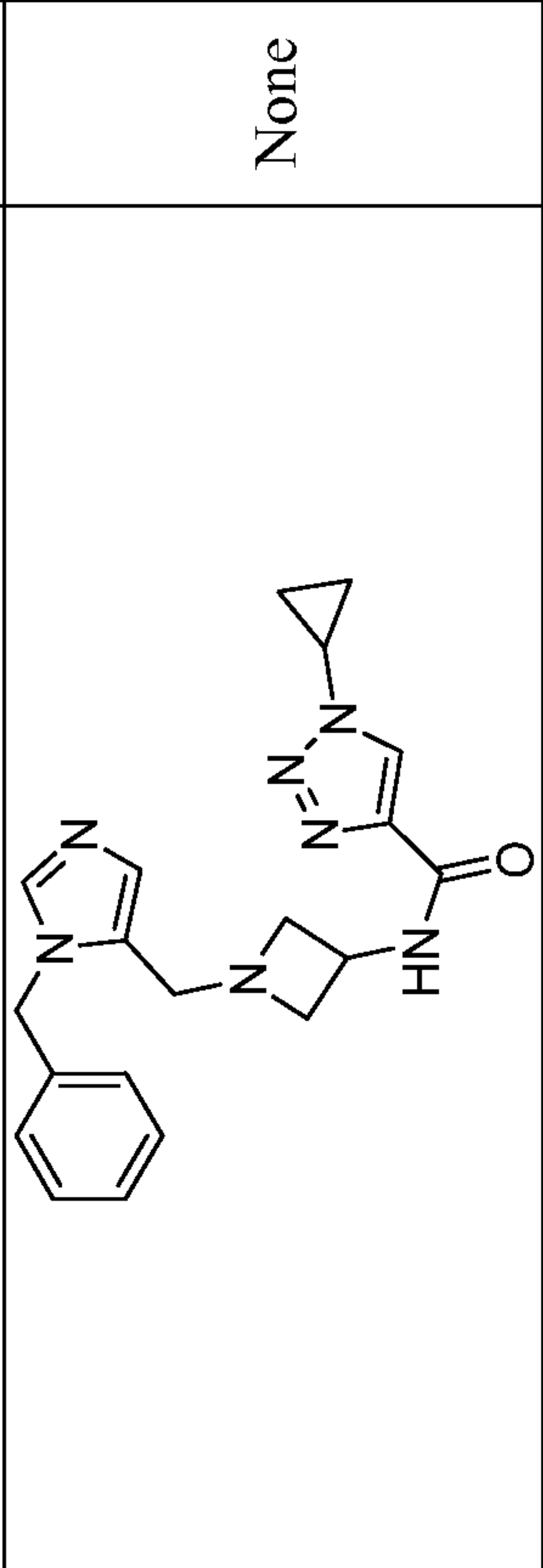
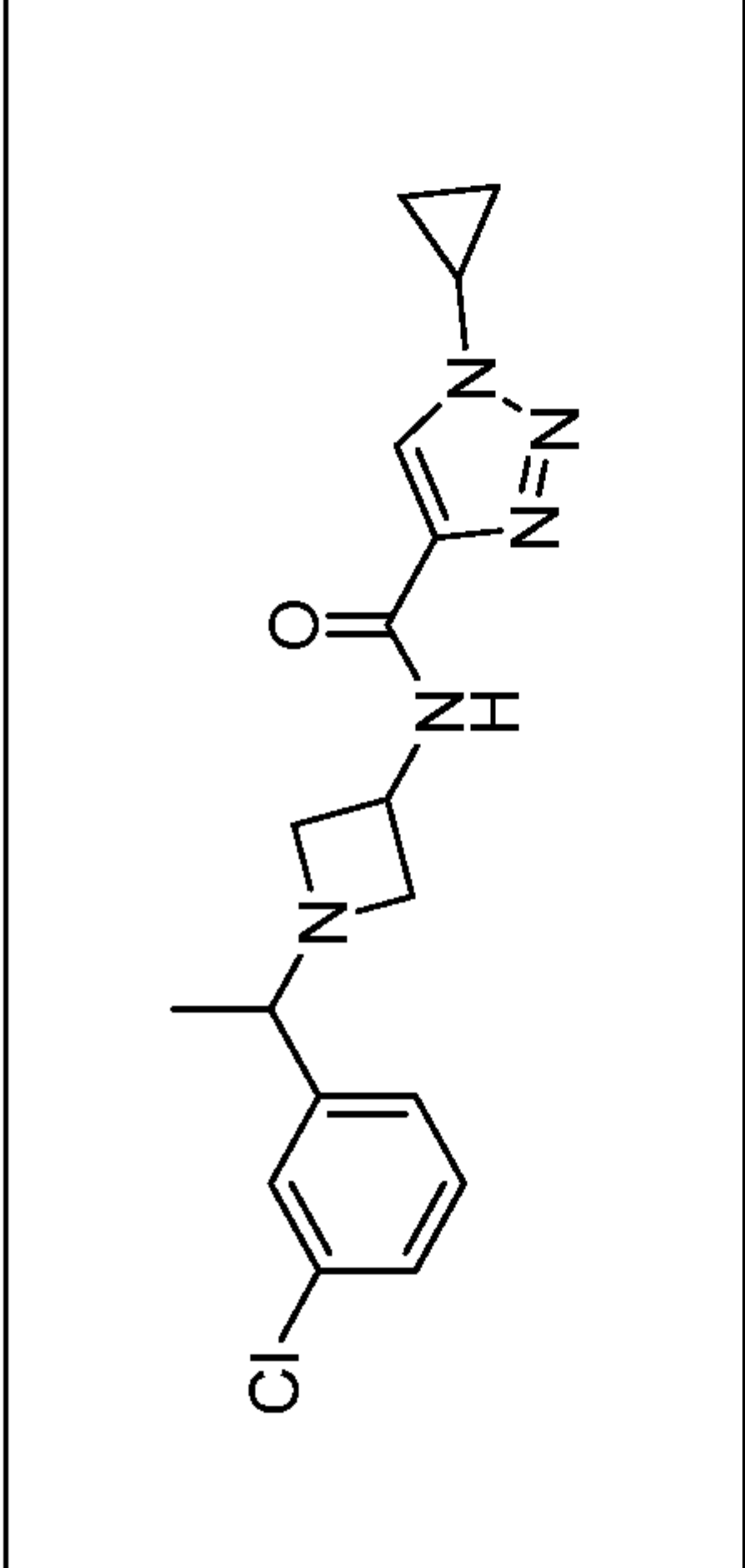
669		None	783		None
670		None	784		None
671		None	785		None
672		None	786		None
673		None	787		None

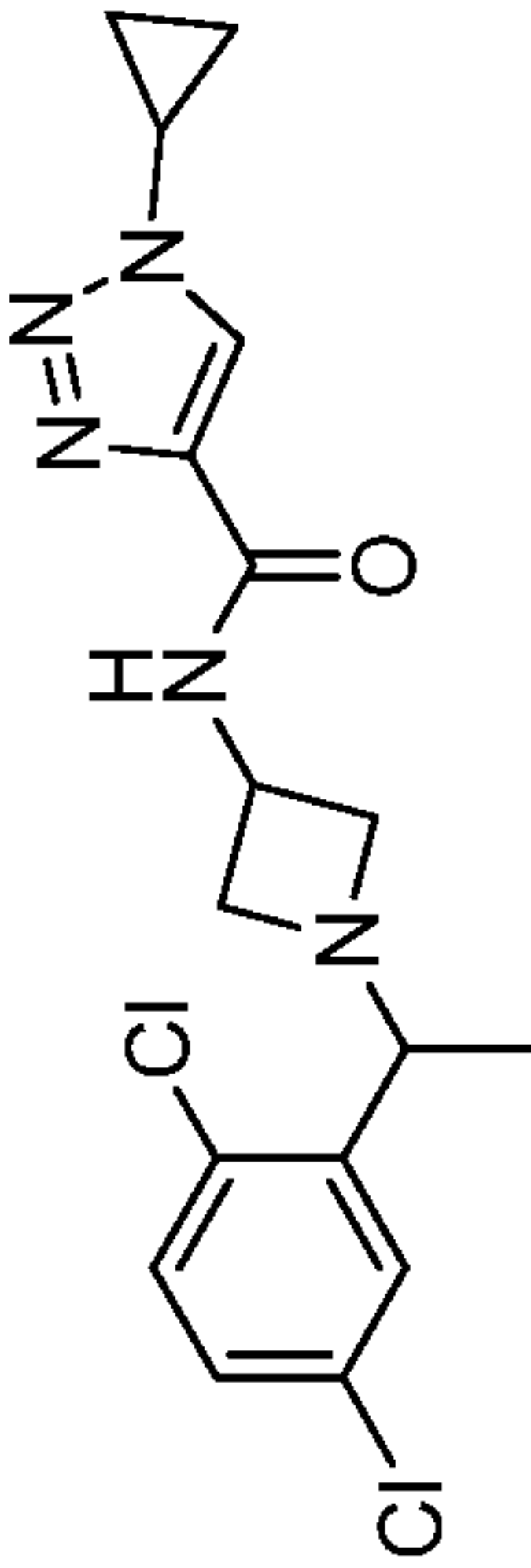
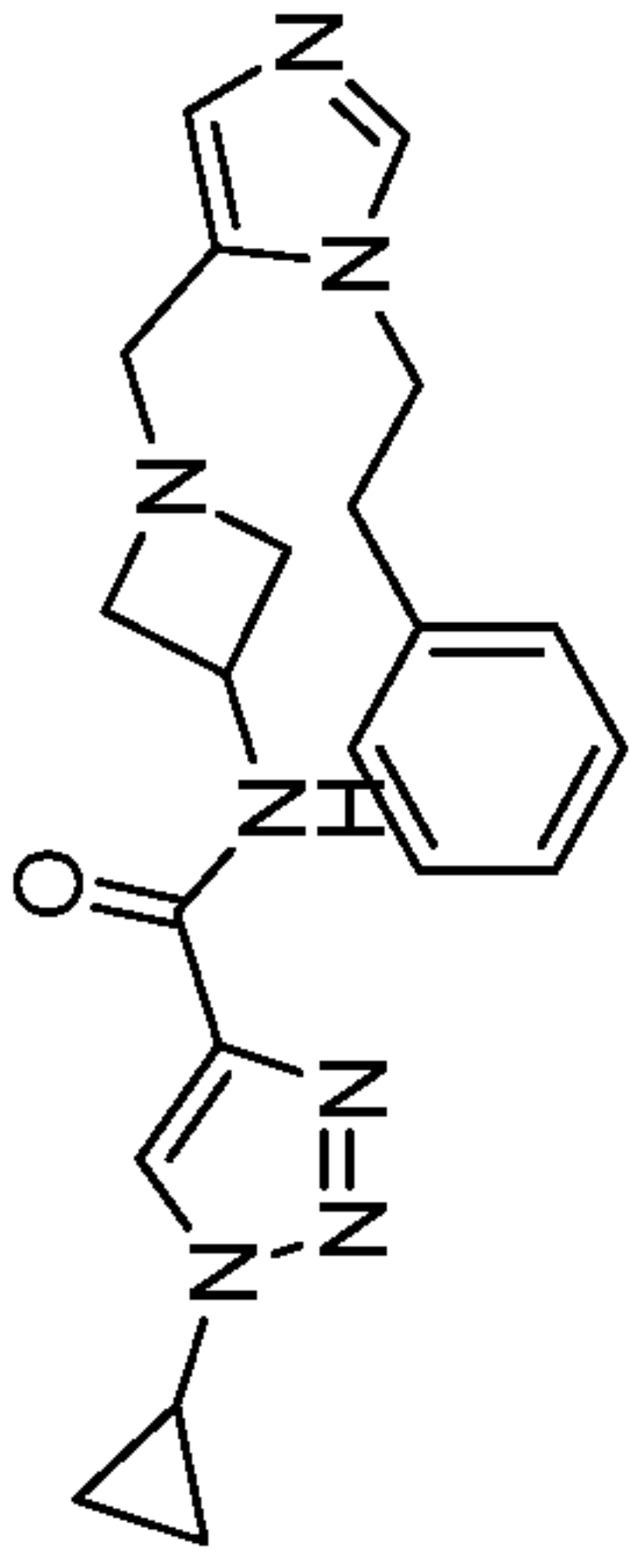
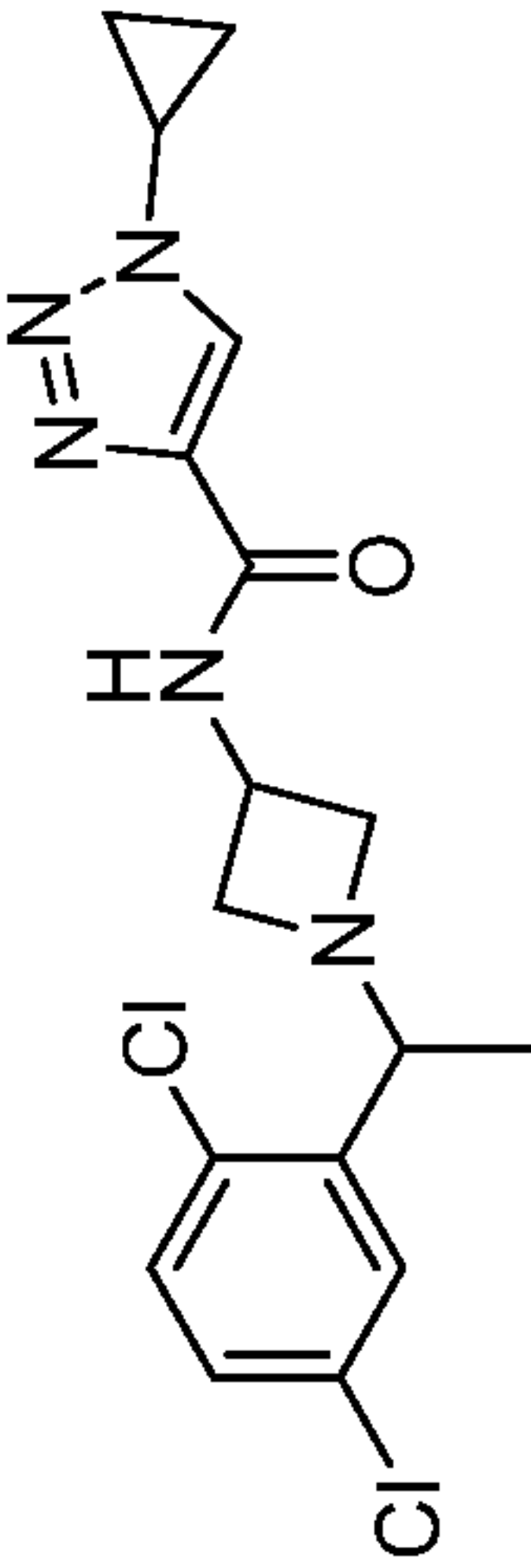
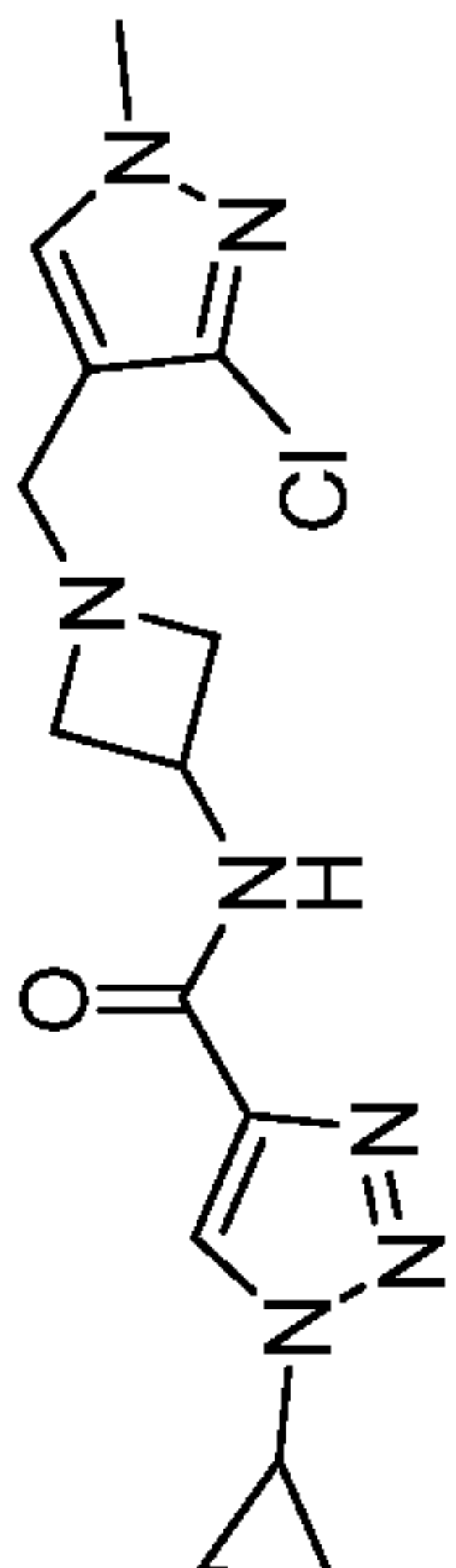
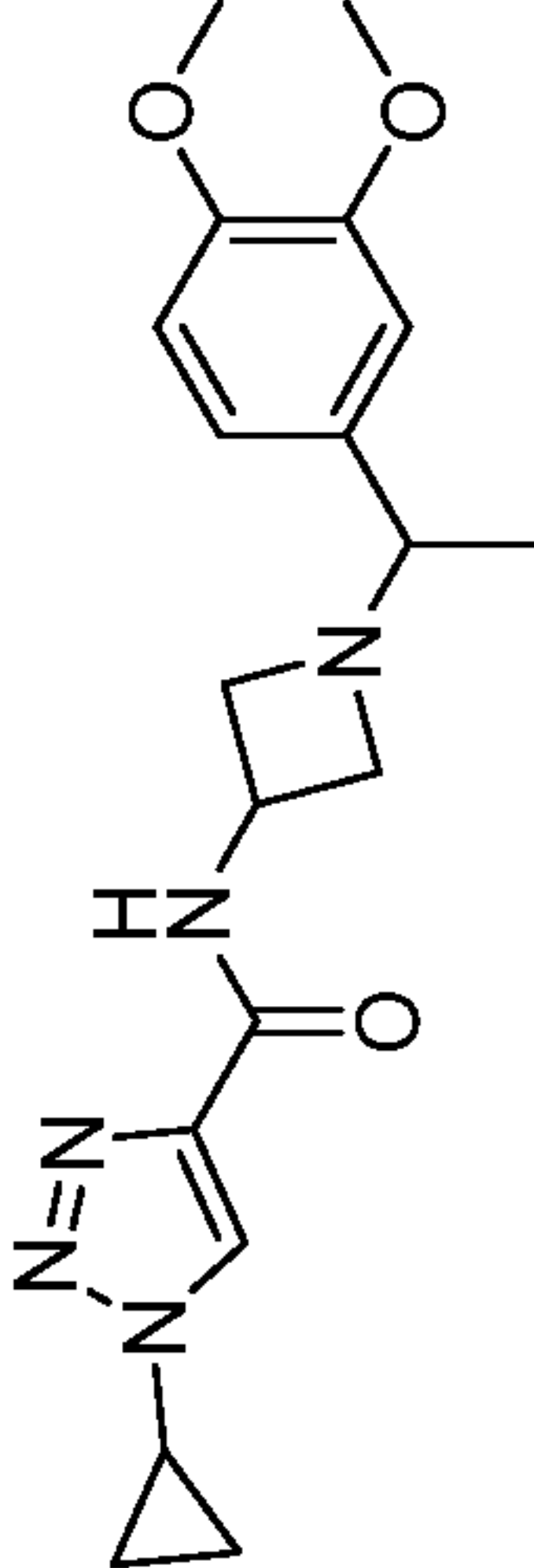
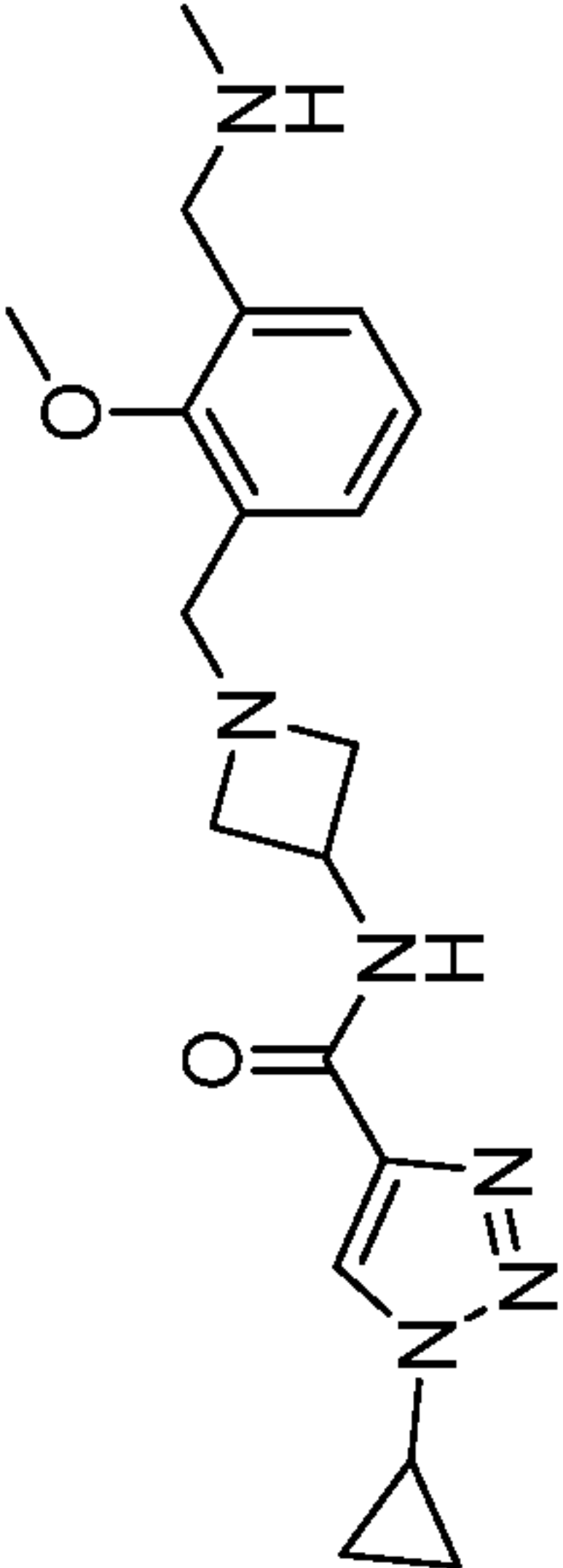
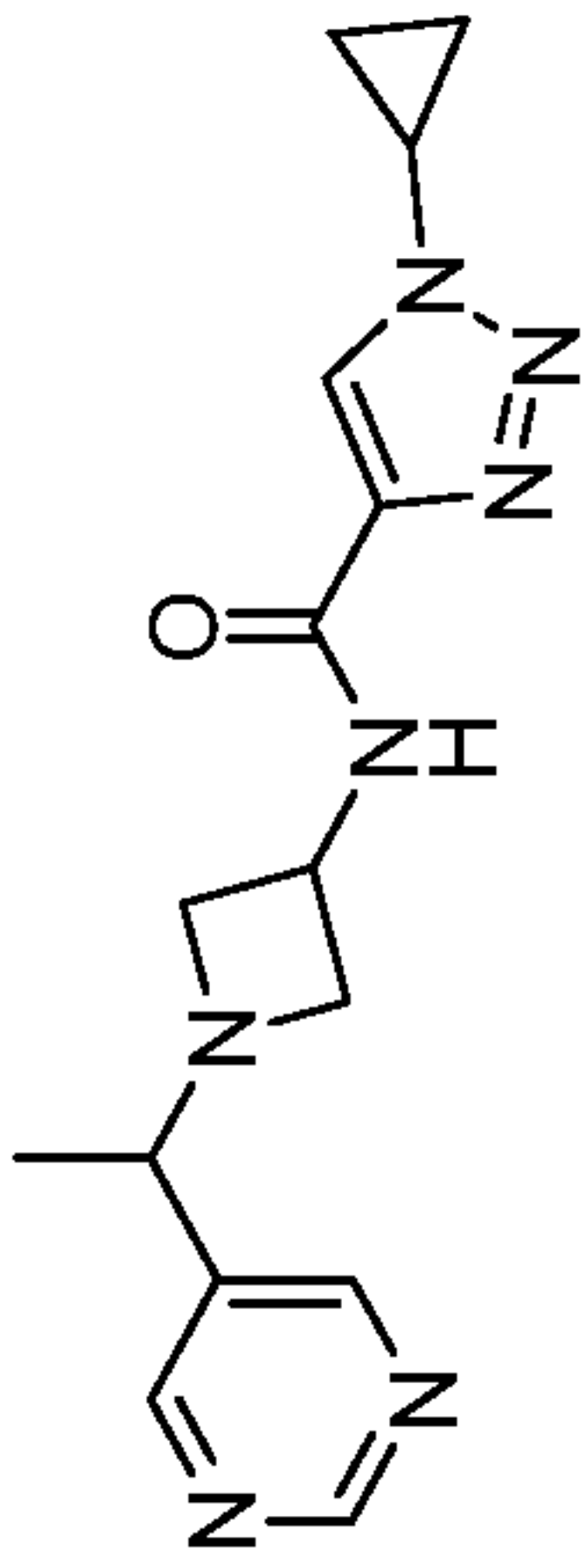
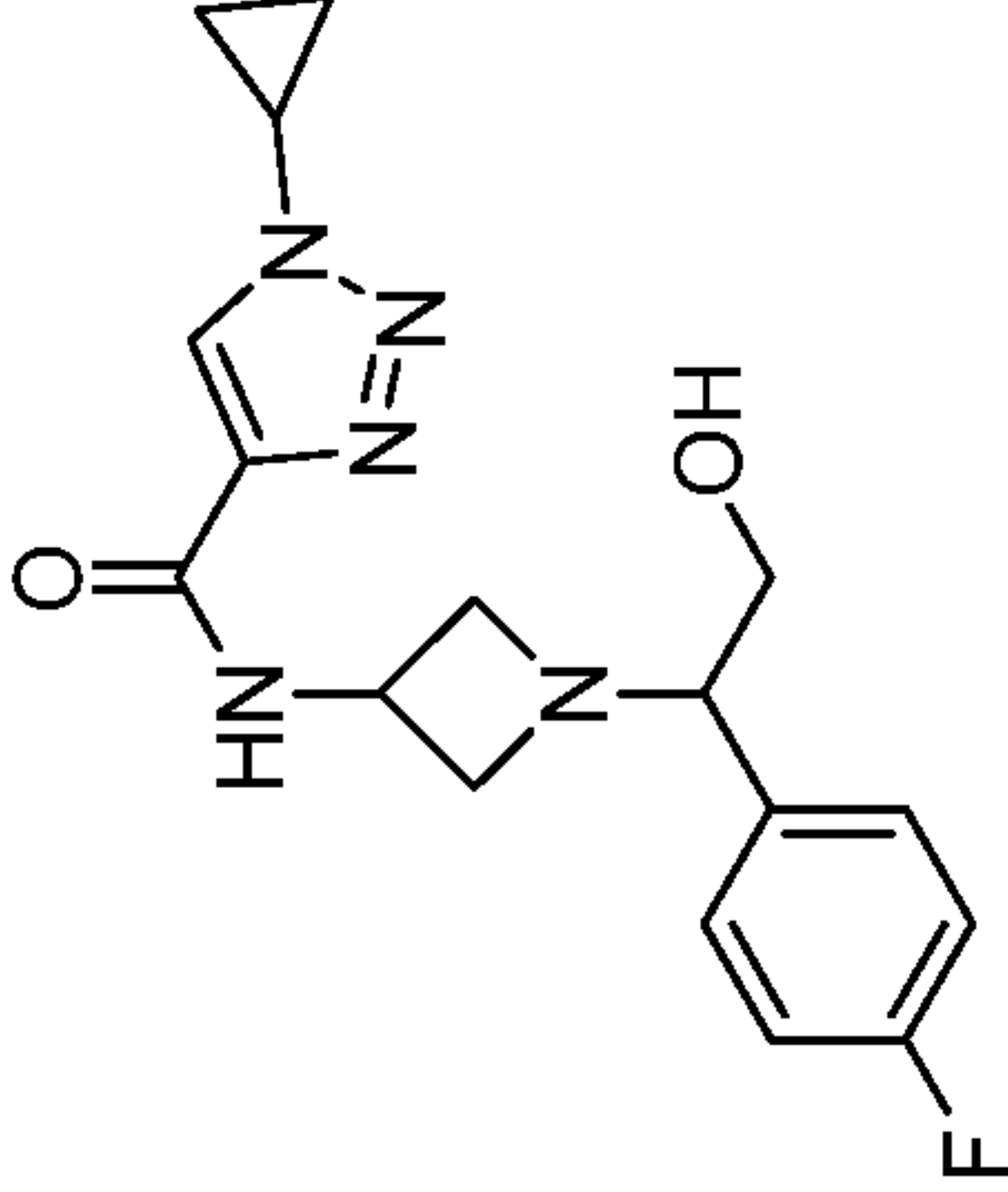
674		None	788		None
675		None	789		None
676		None	790		None
677		None	791		None

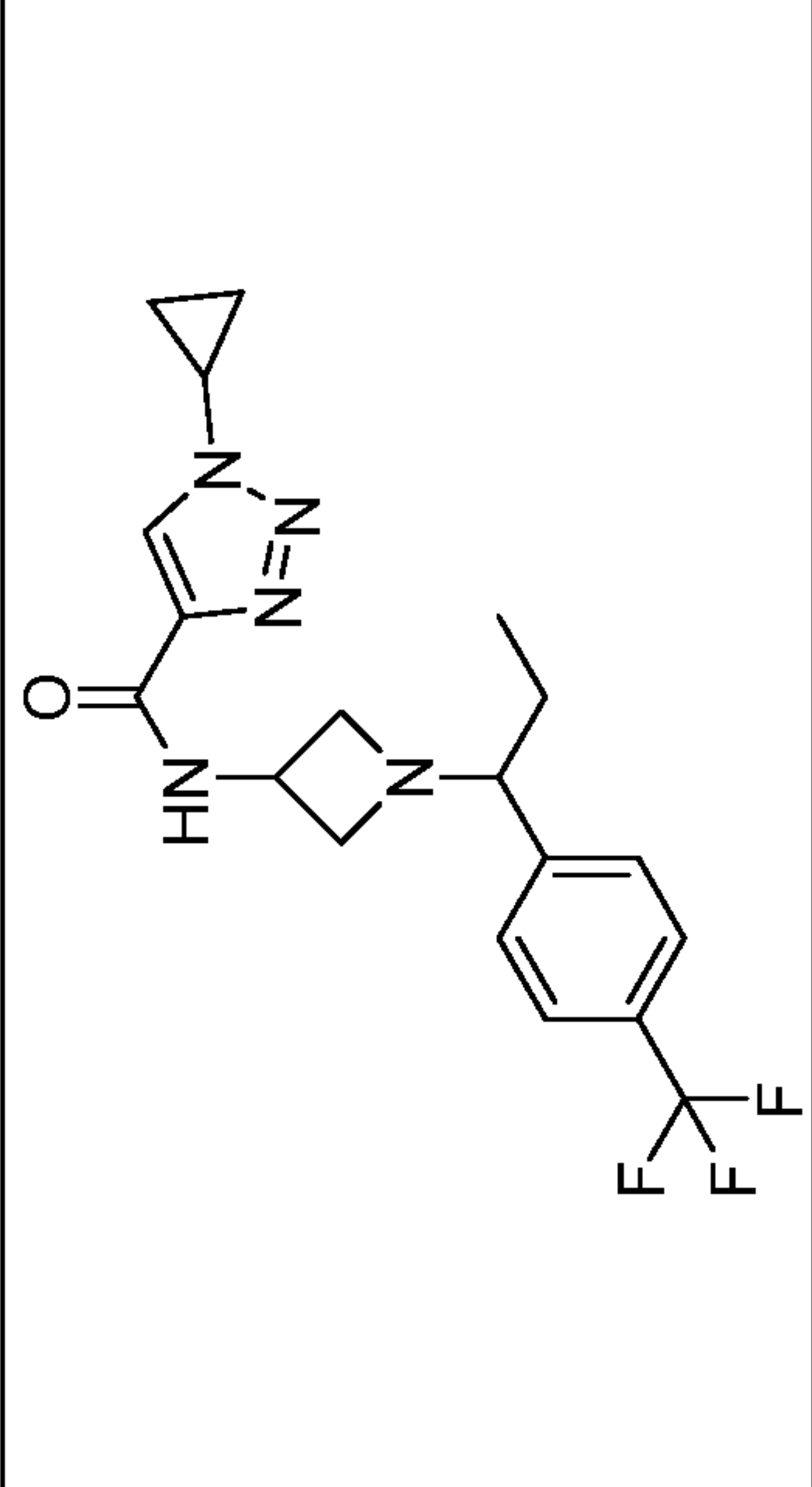
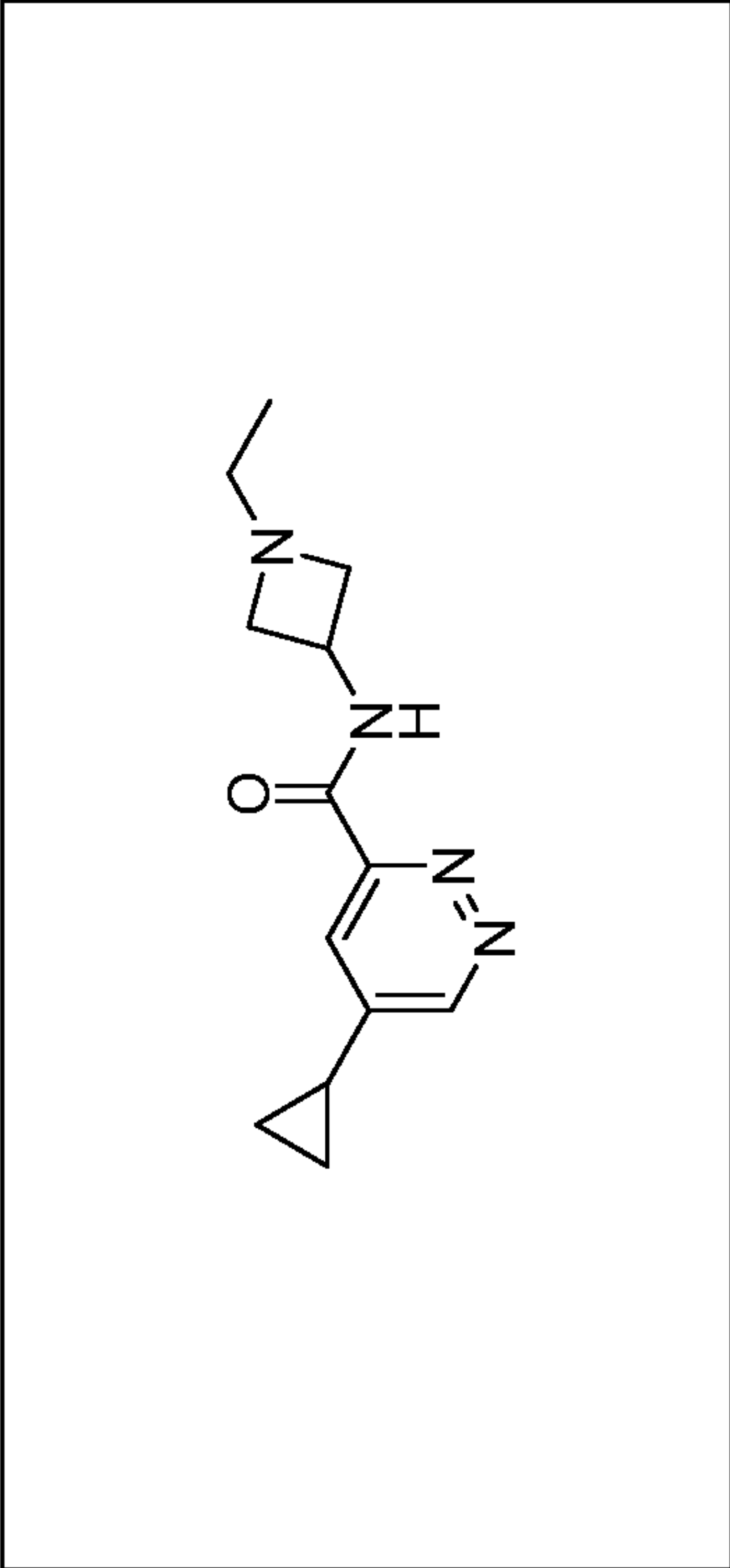
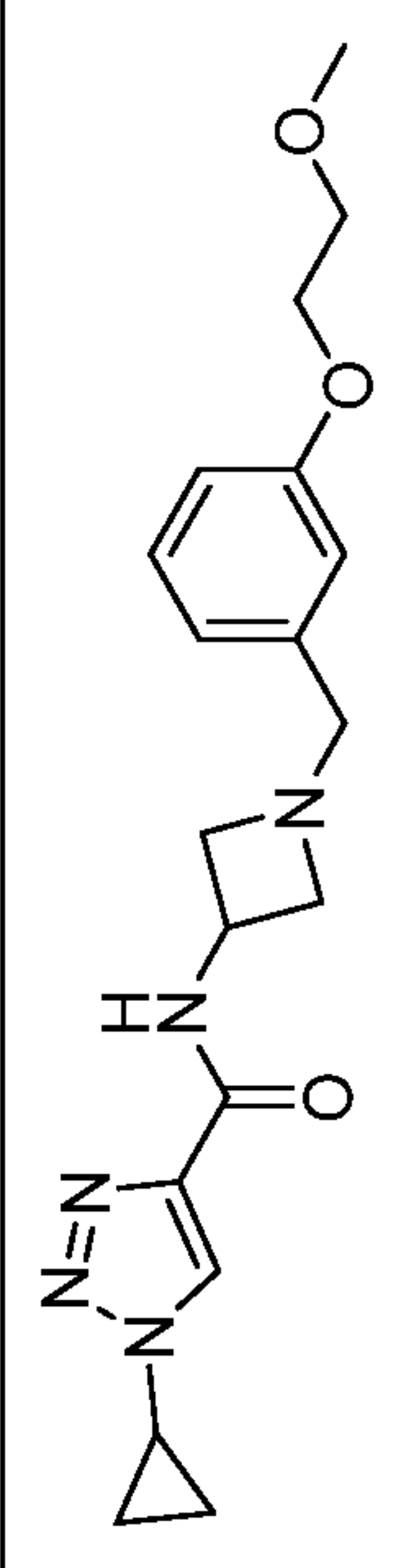
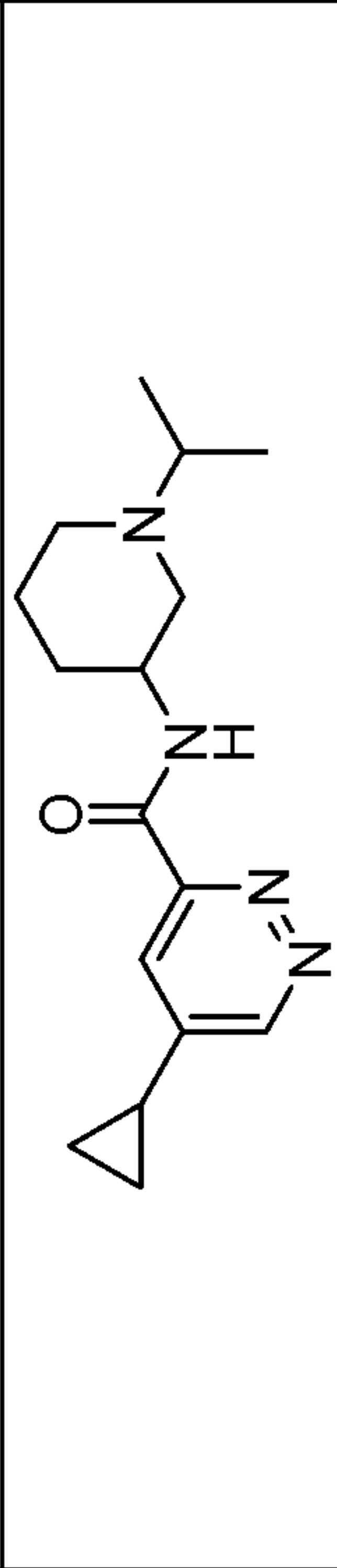
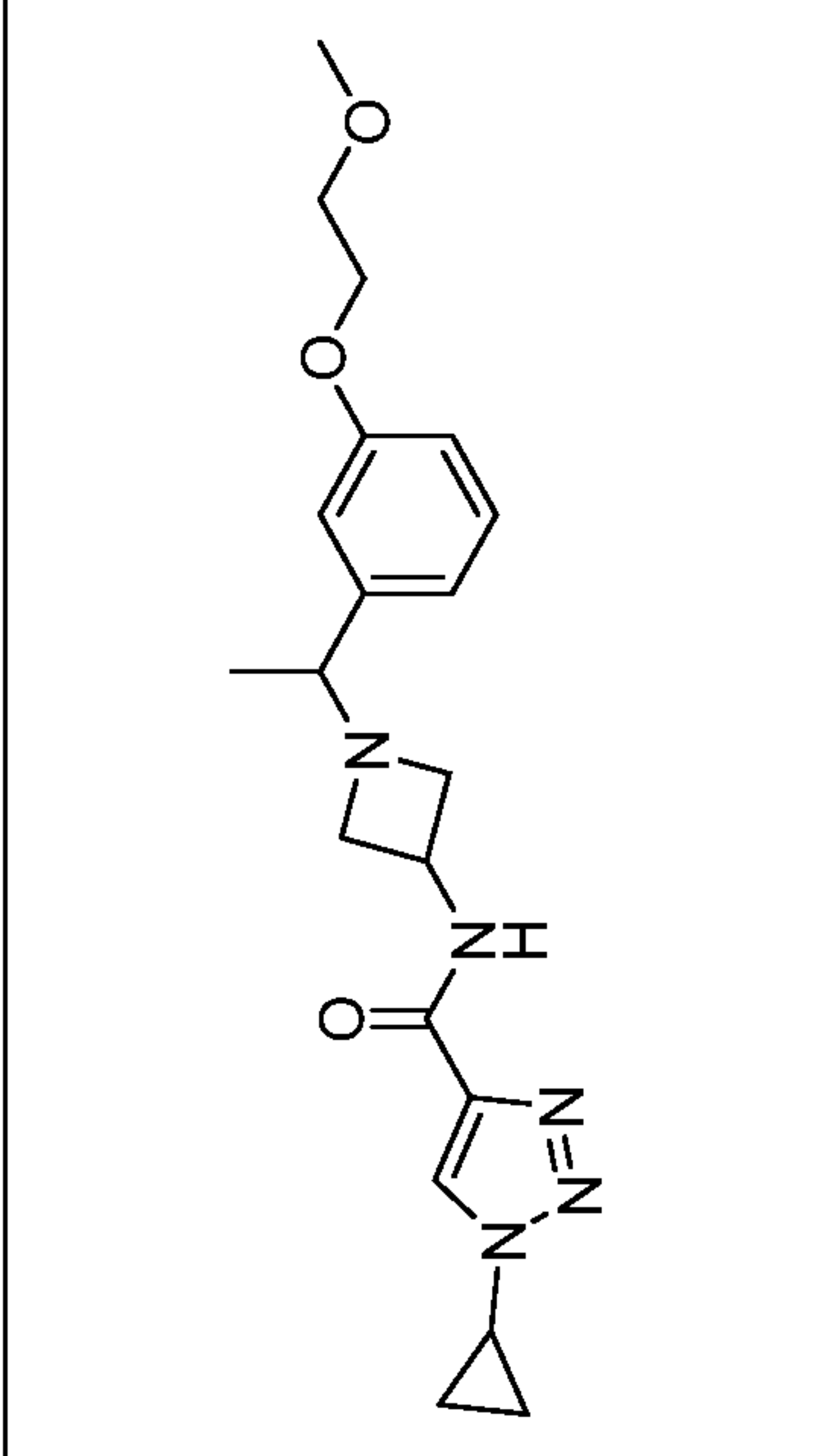
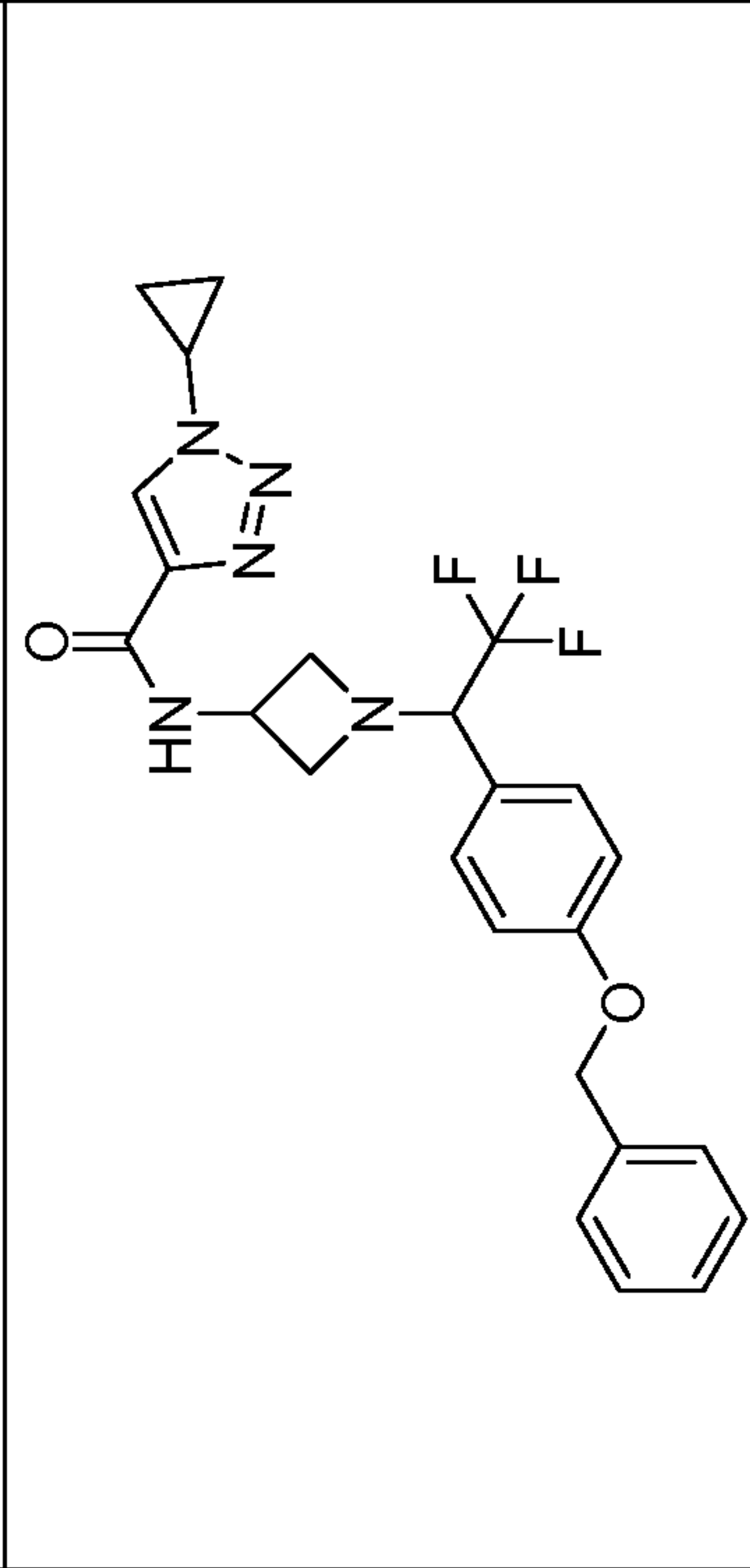
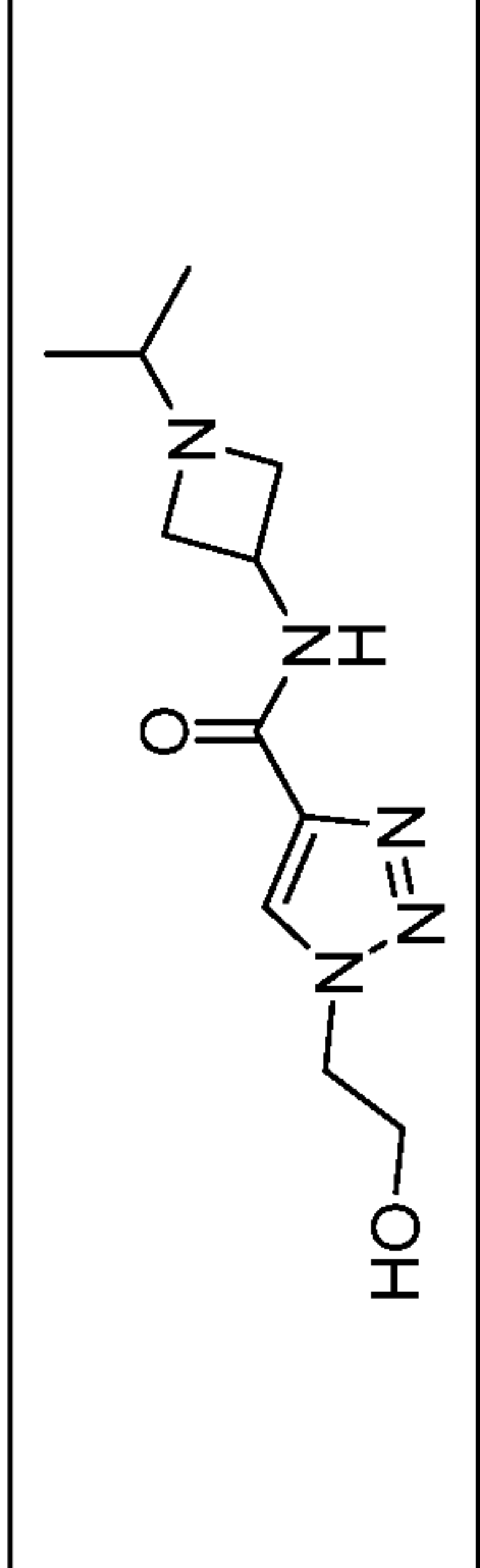
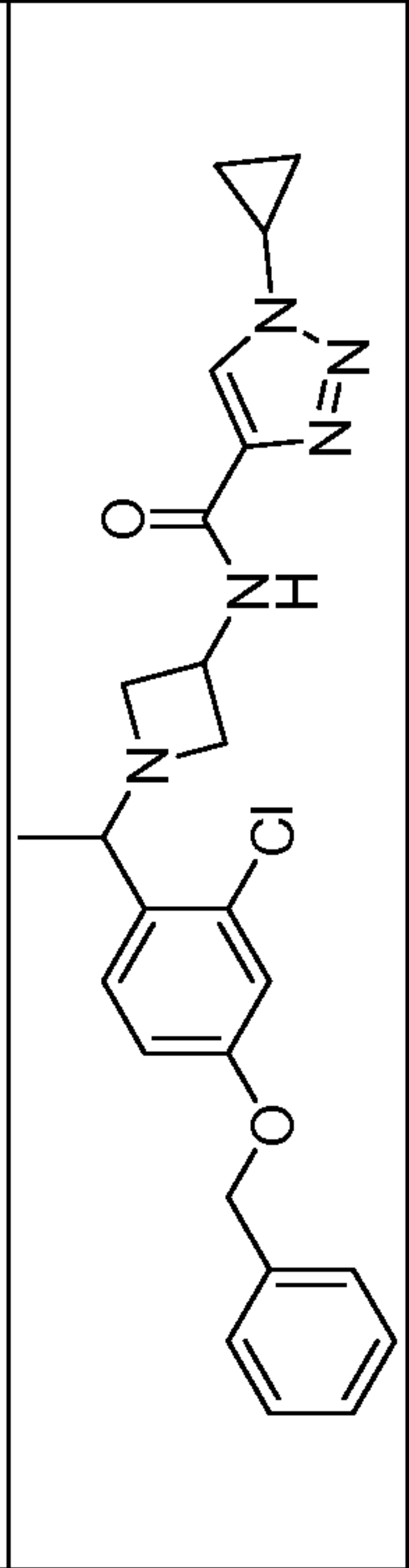
678		None	792		None
679		None	793		None
680		None	794		None
681		None	795		None

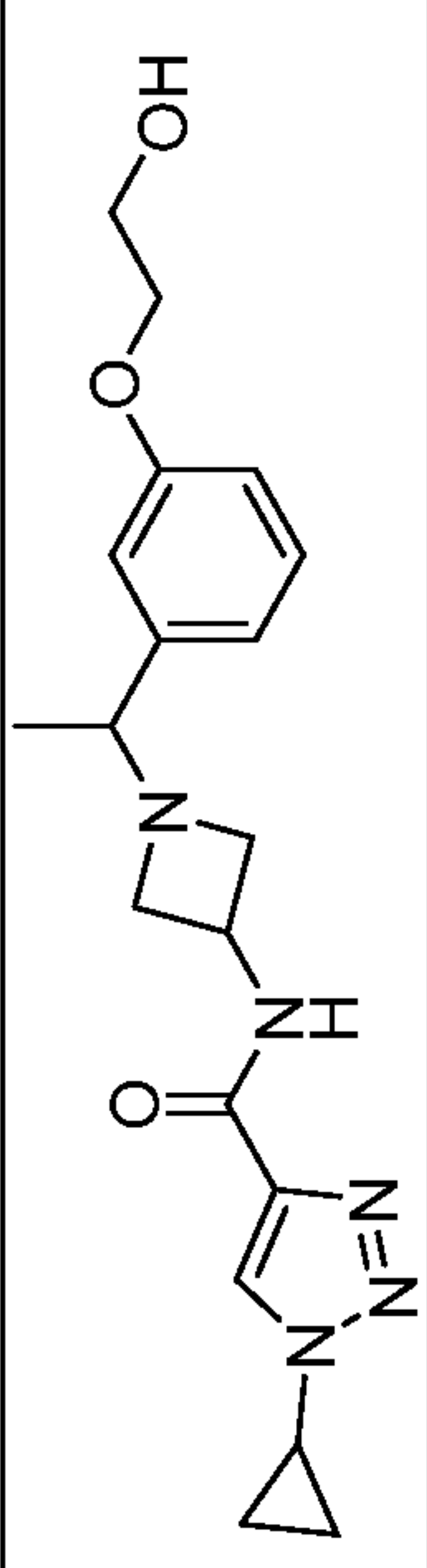
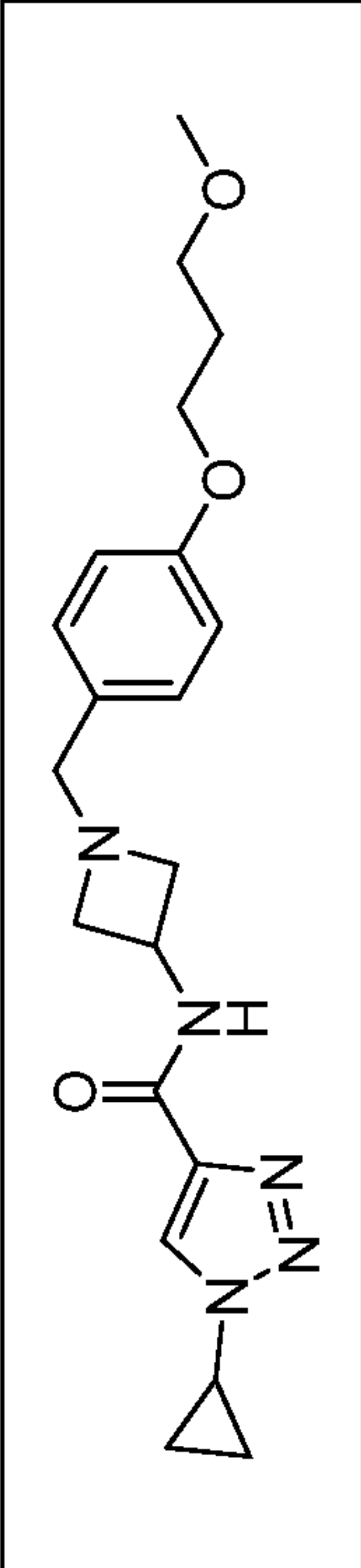
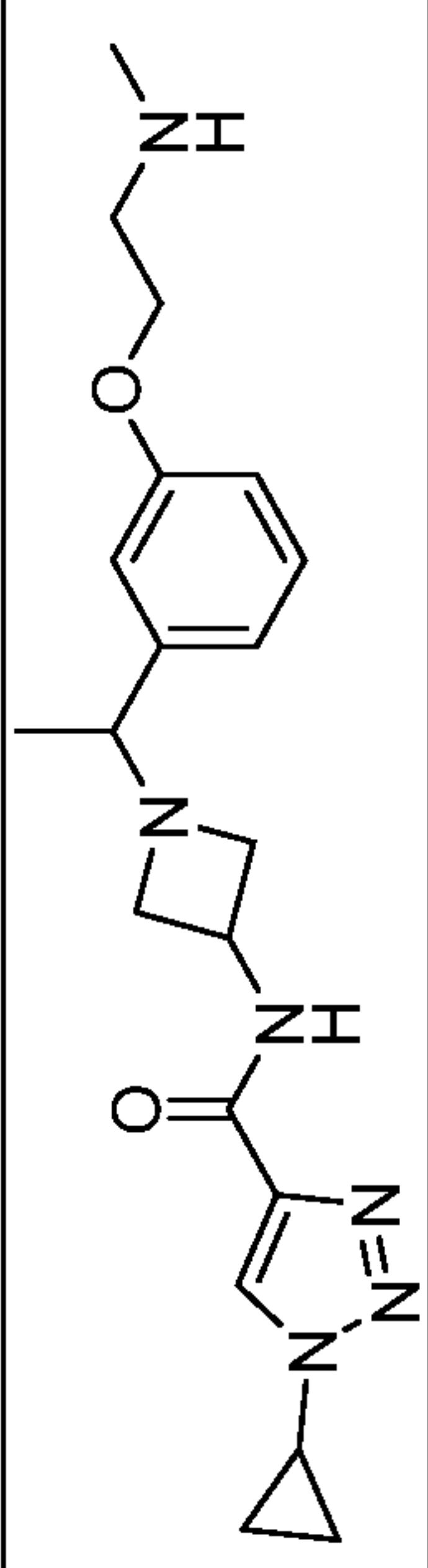
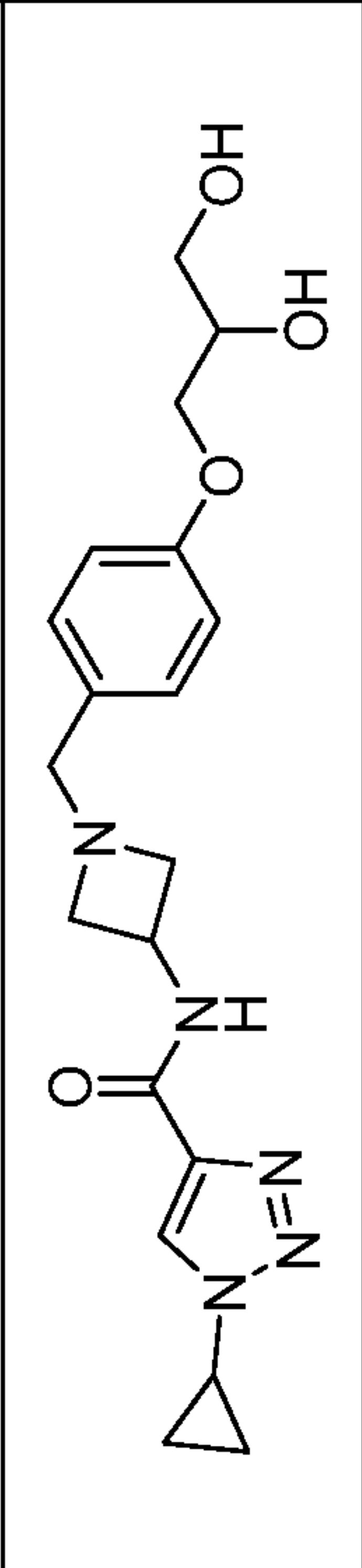
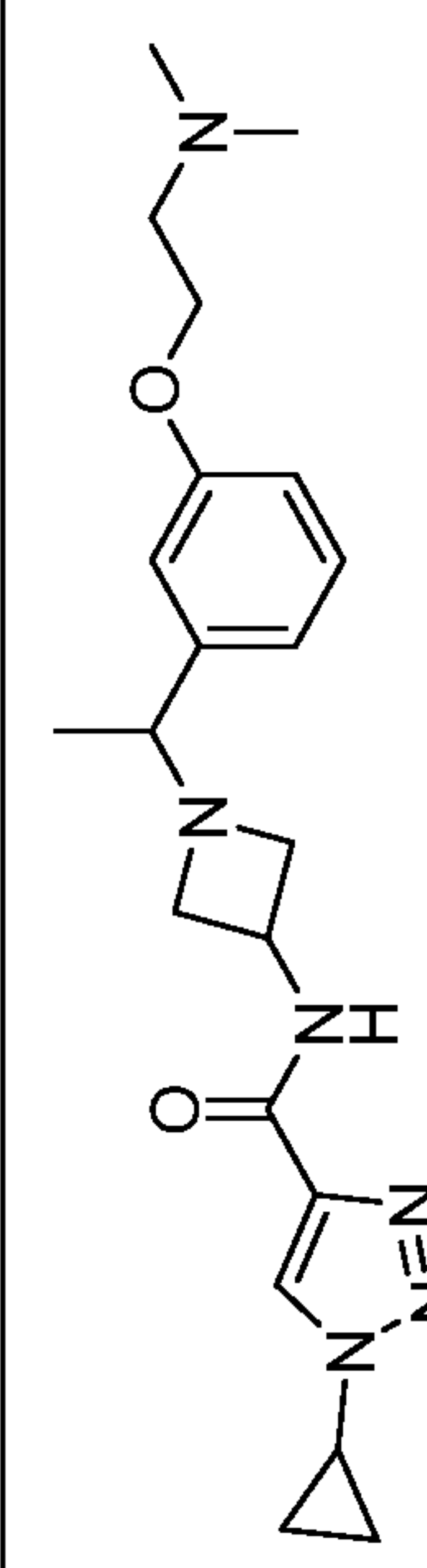
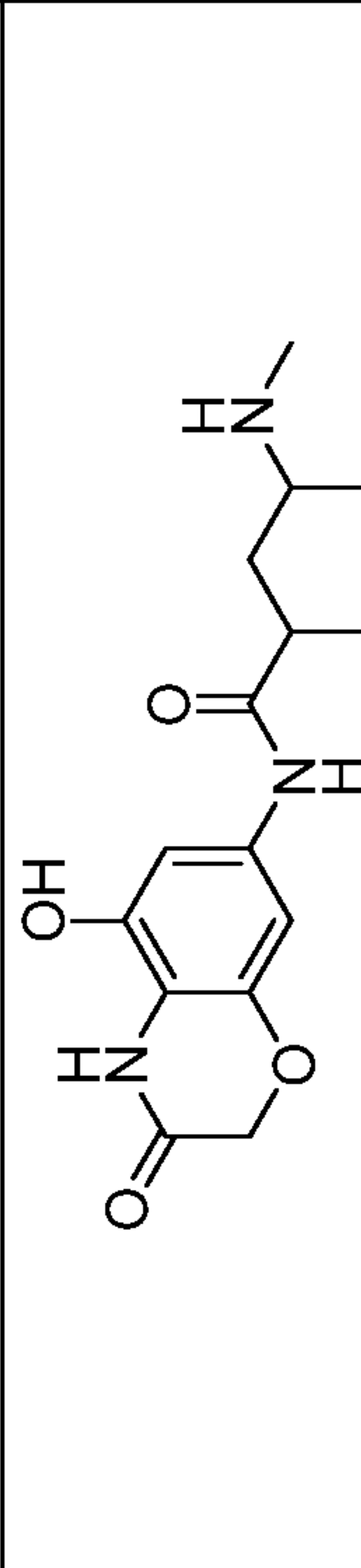
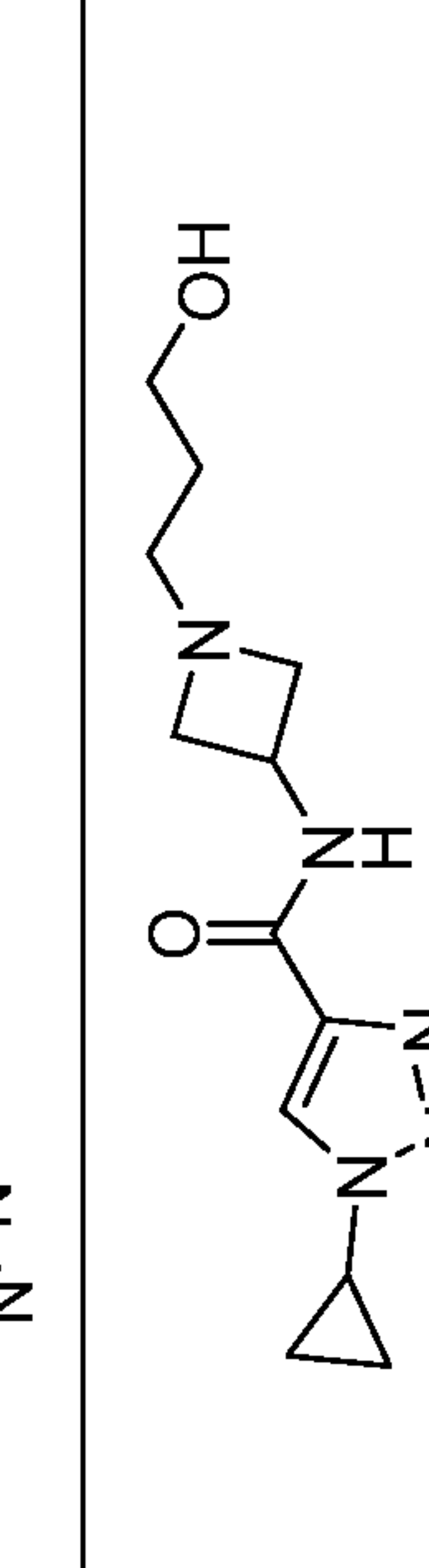
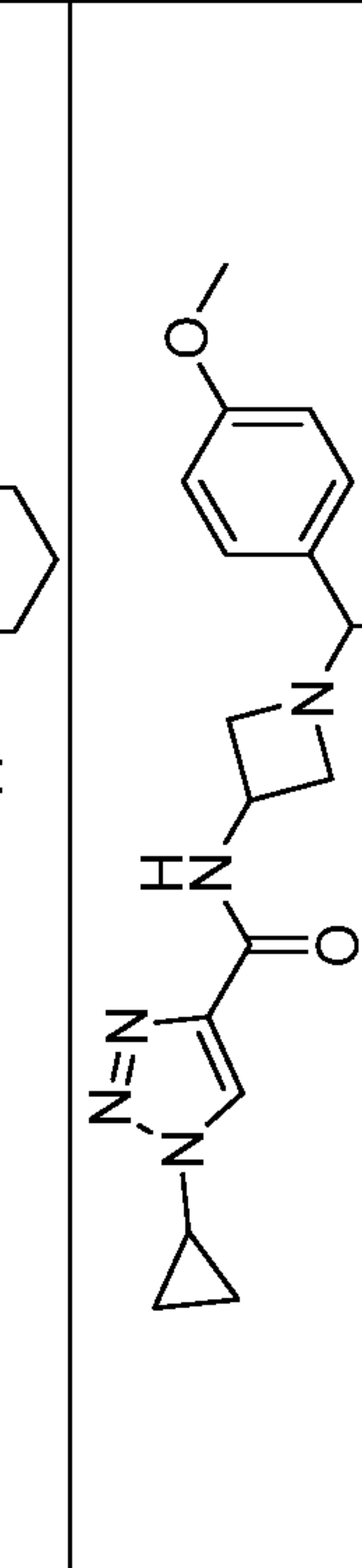
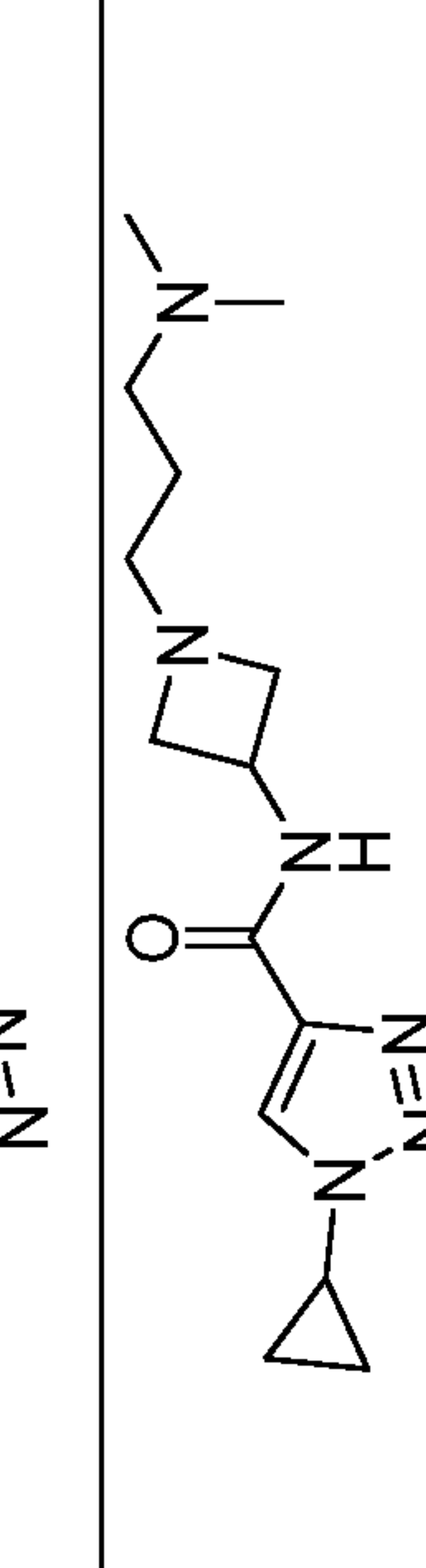
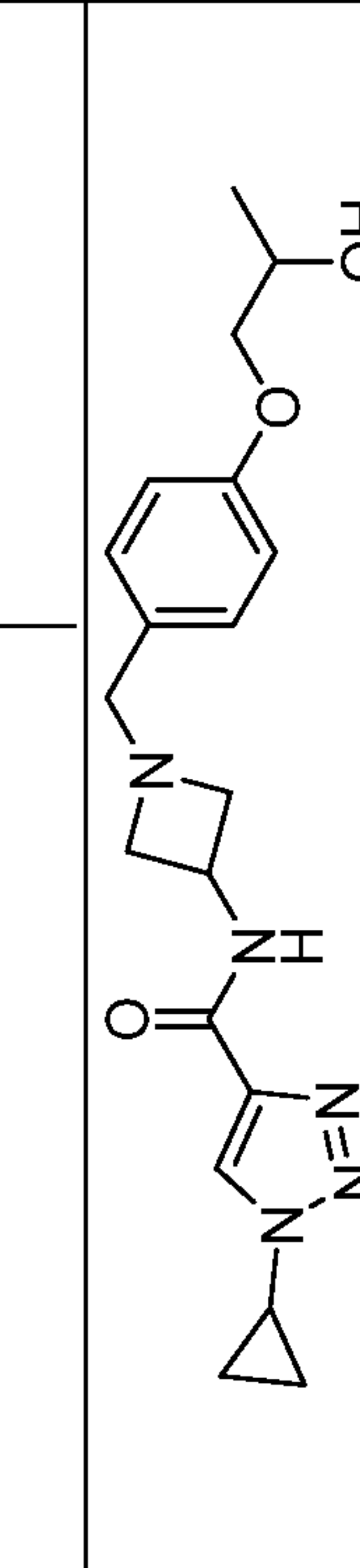
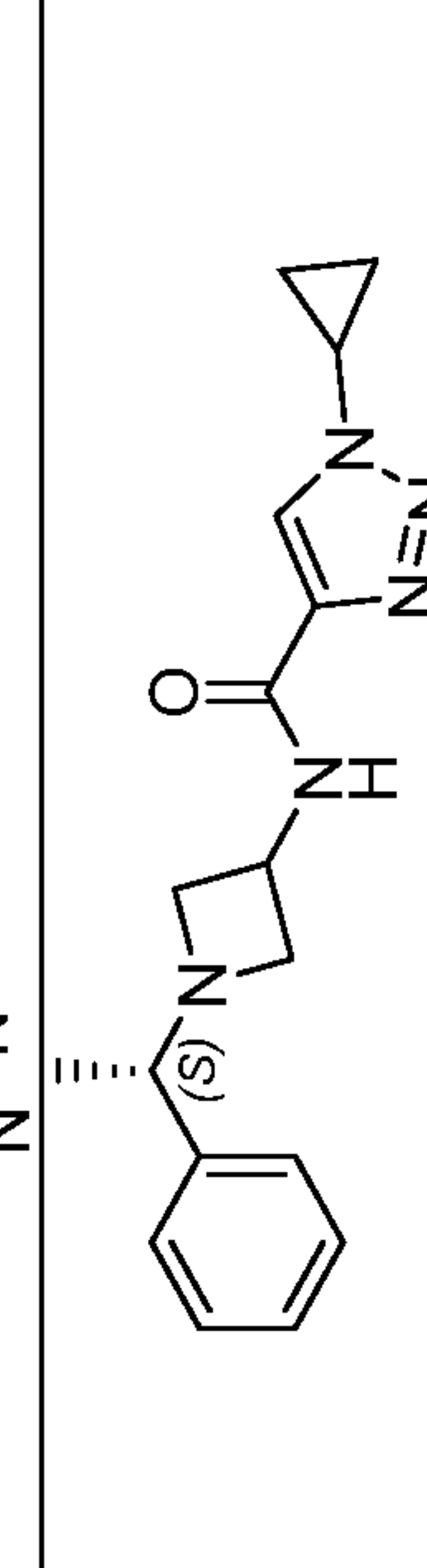
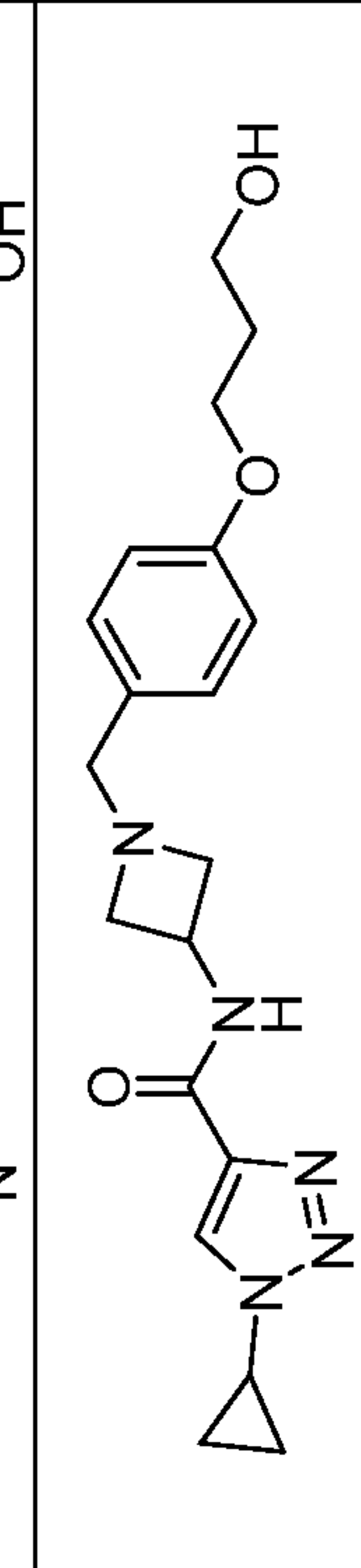
682		None	796		None
683		None	797		None
684		None	798		None
685		None	799		None

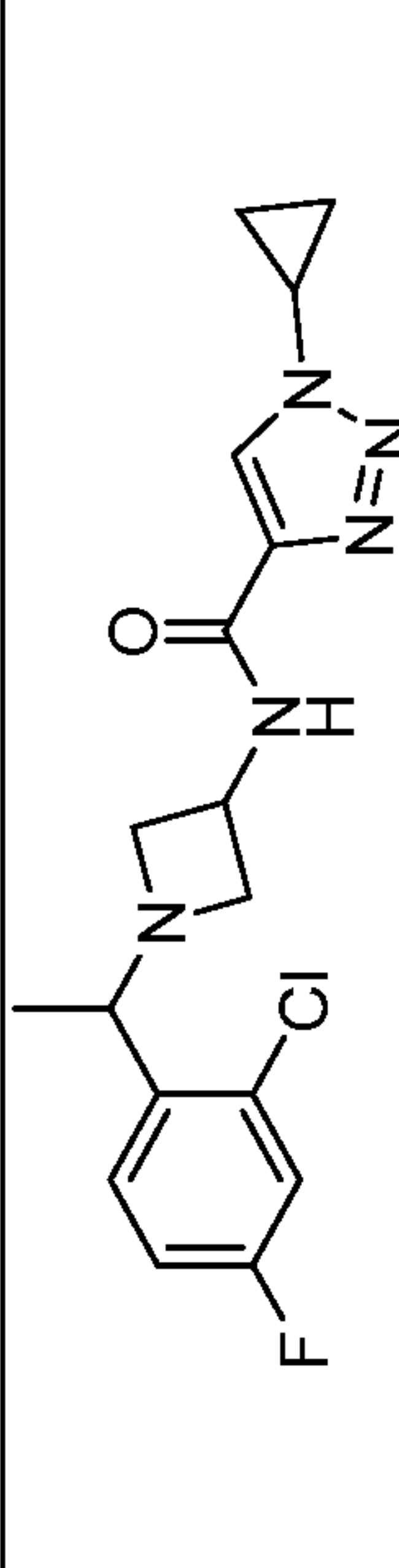
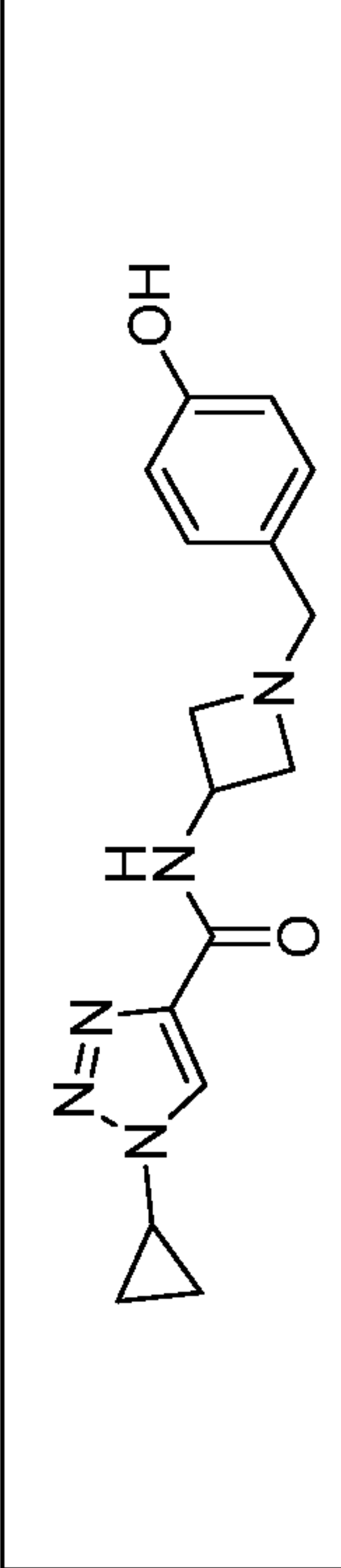
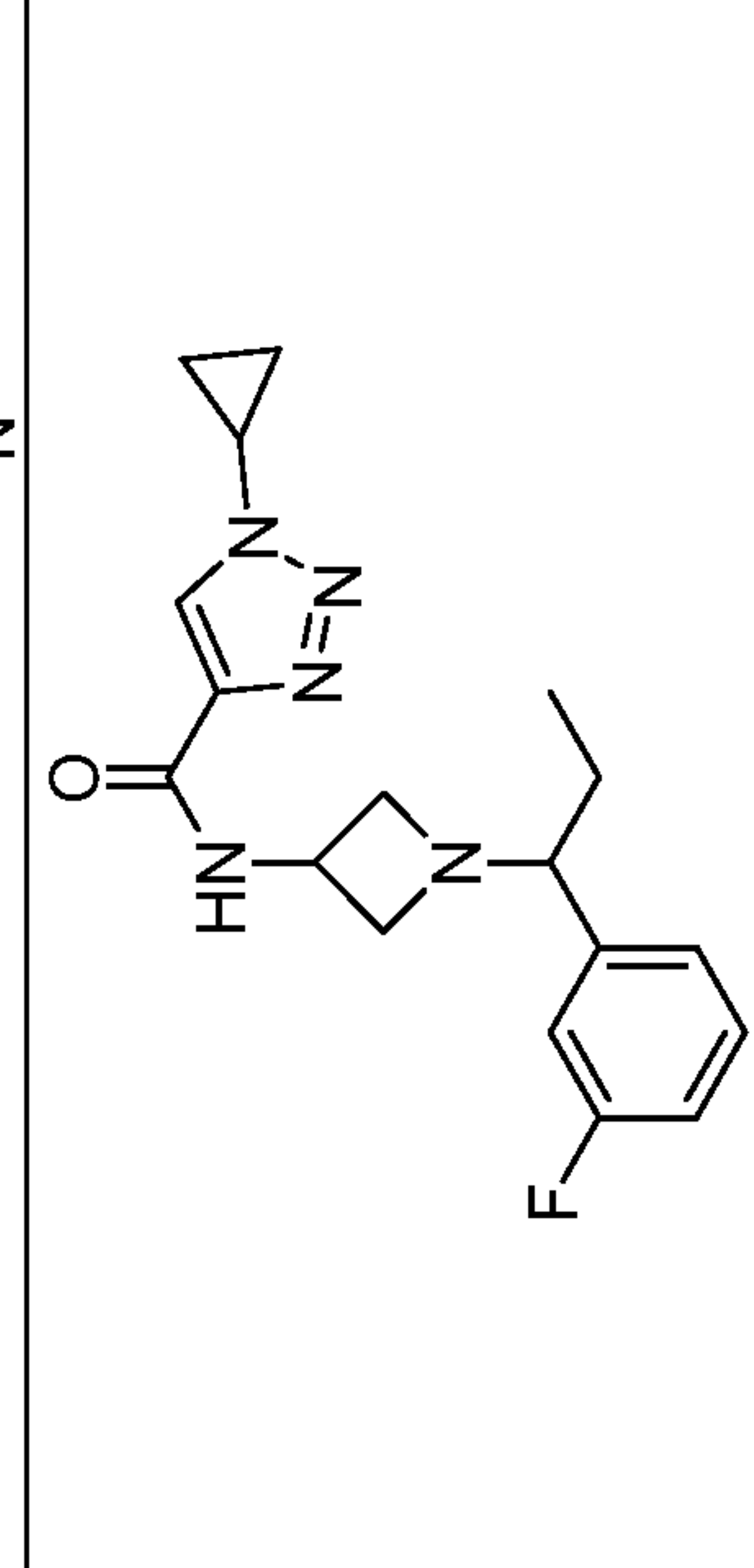
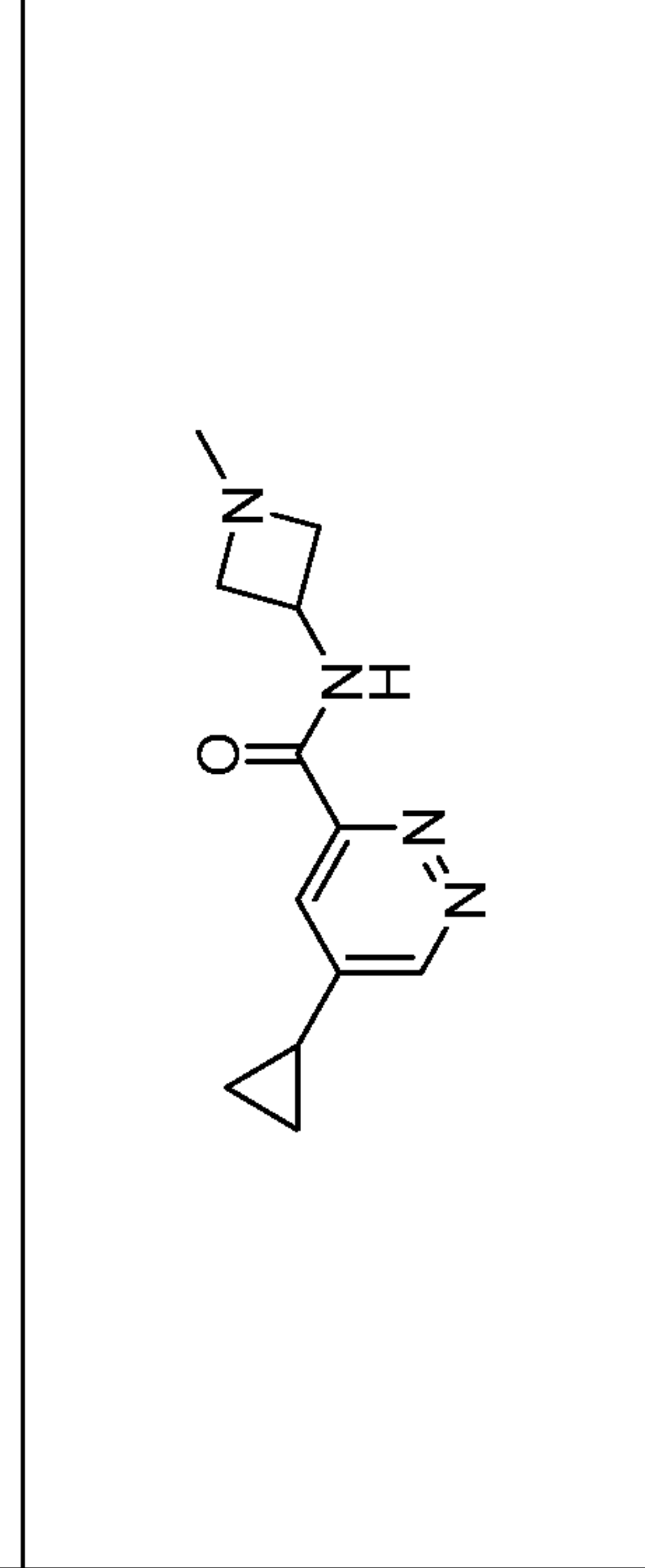
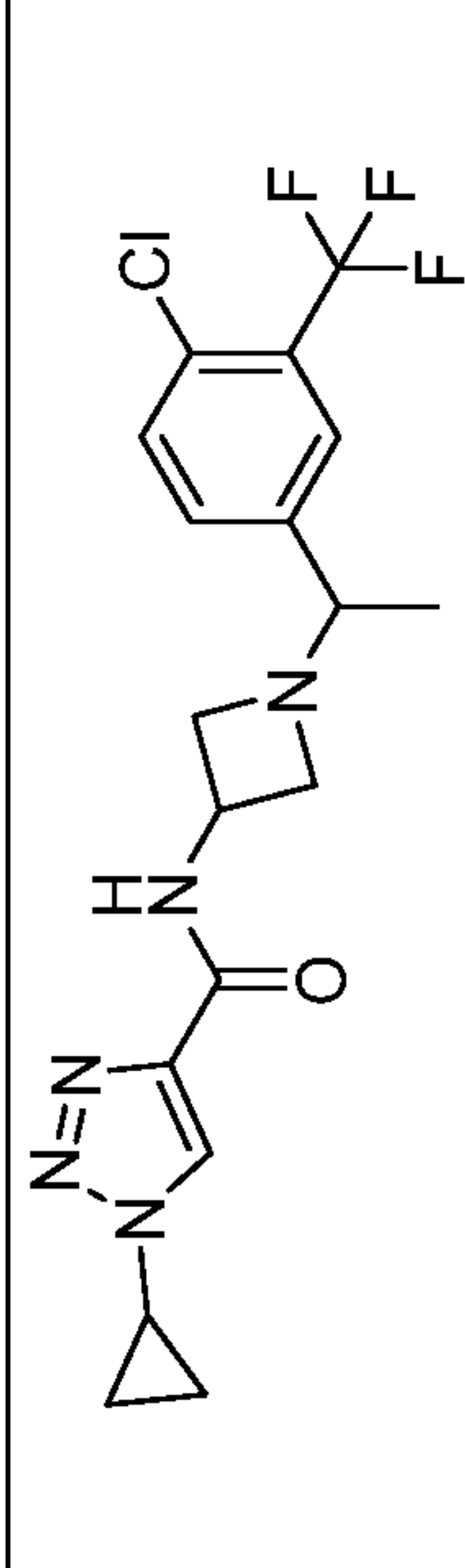
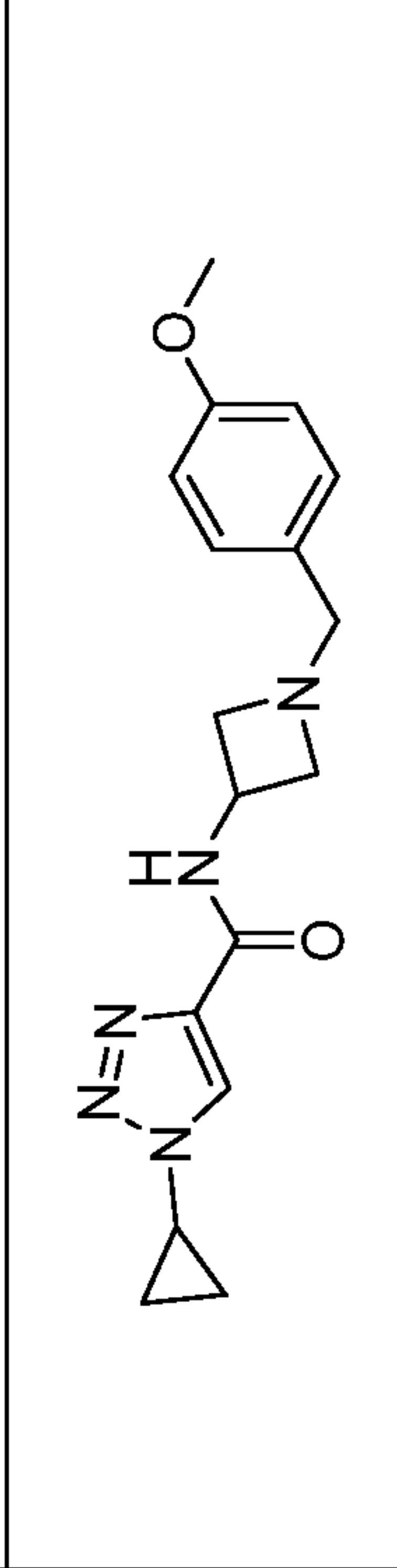
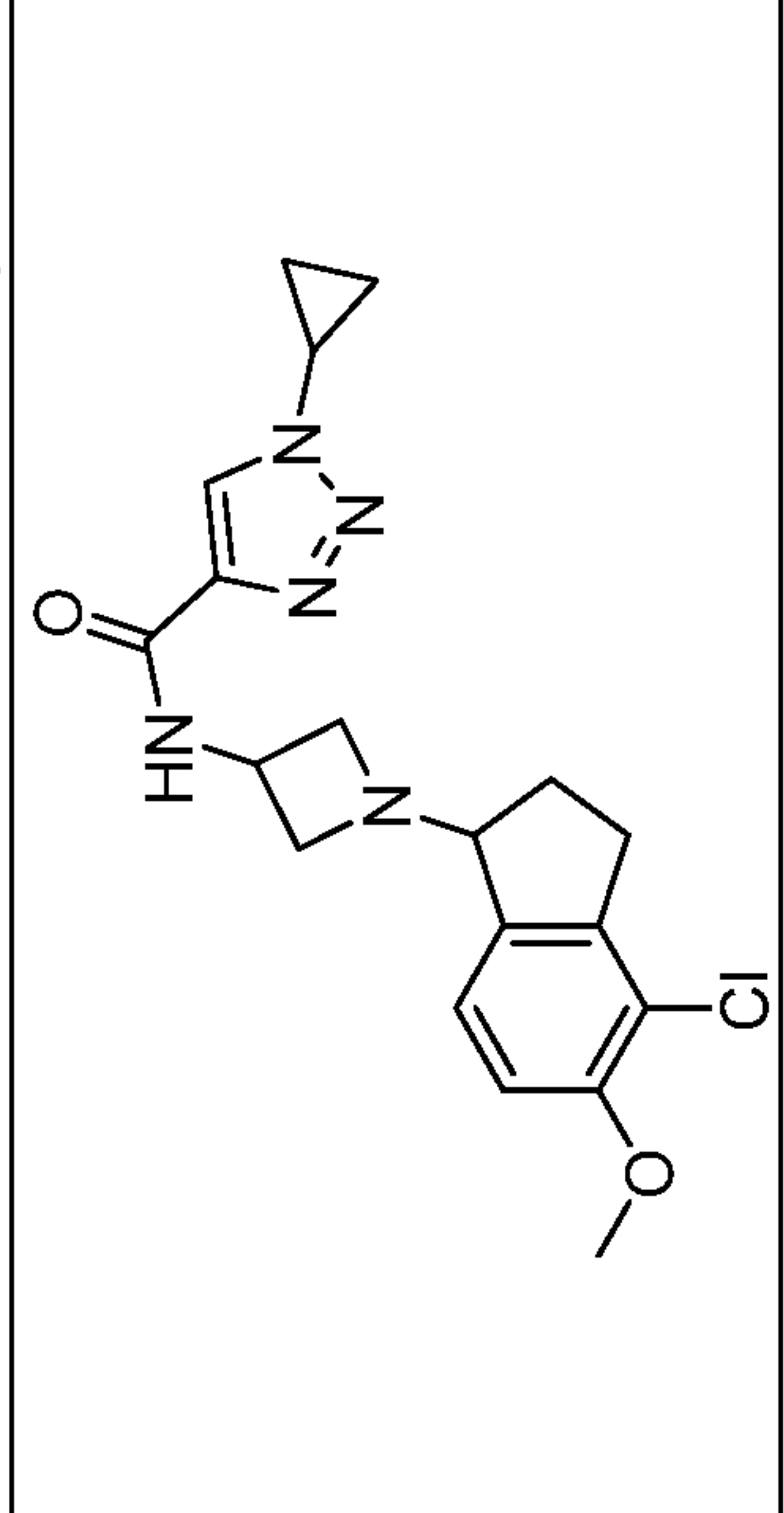
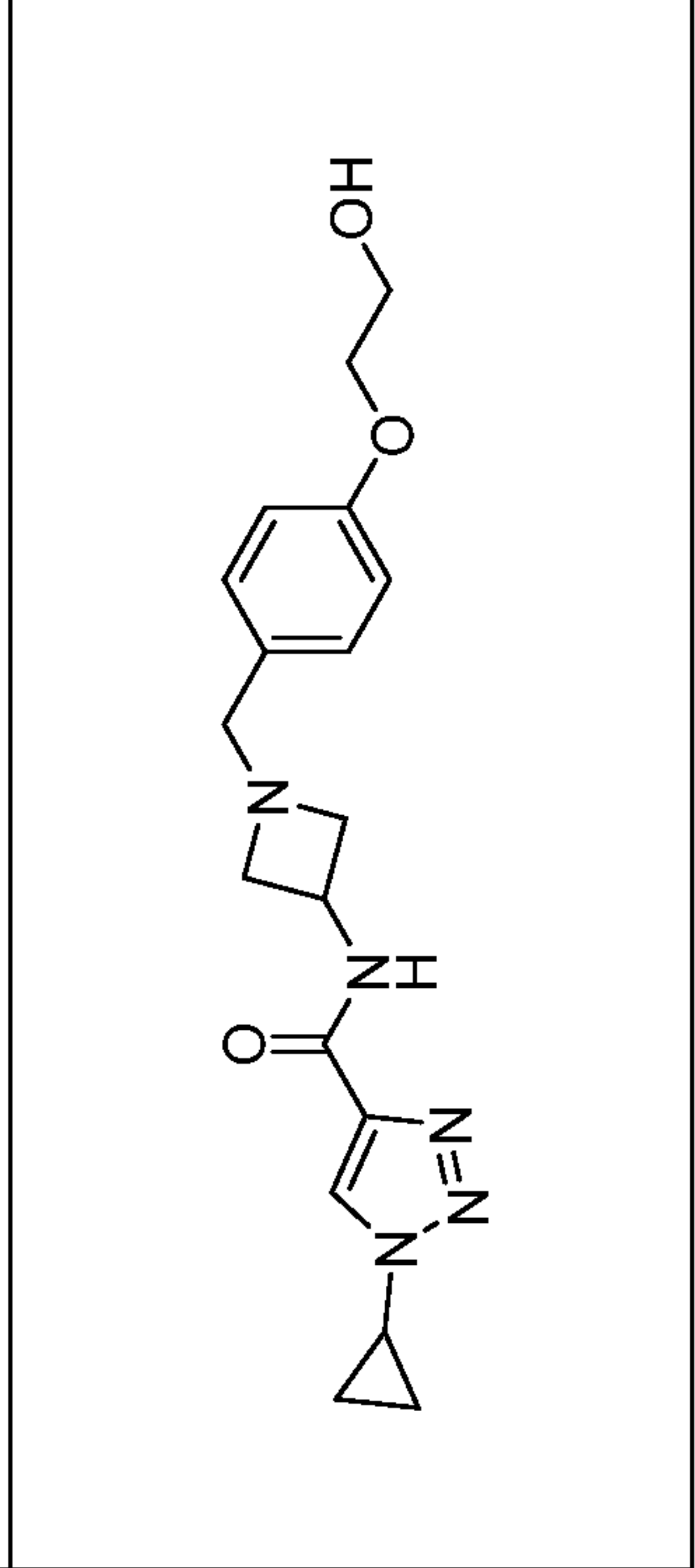
686		None	800		None
687		None	801		None
688		None	802		None
689		None	803		None
690		None	804		None
691		None	805		None

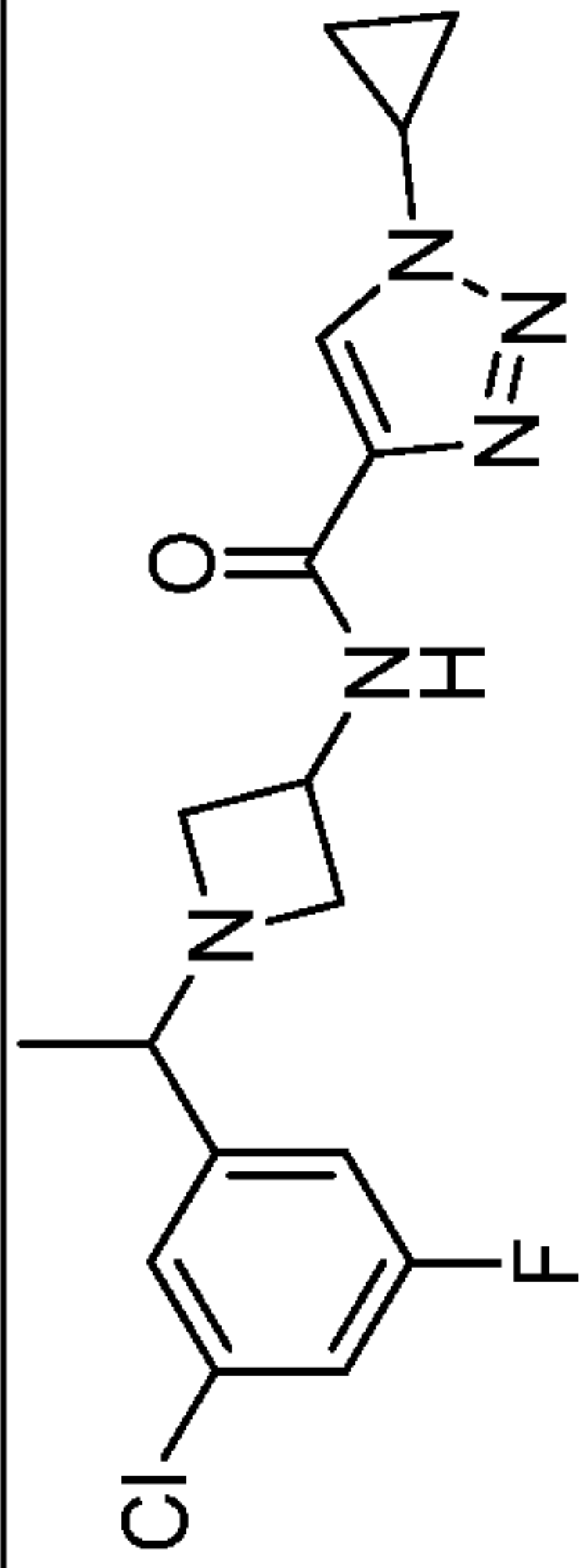
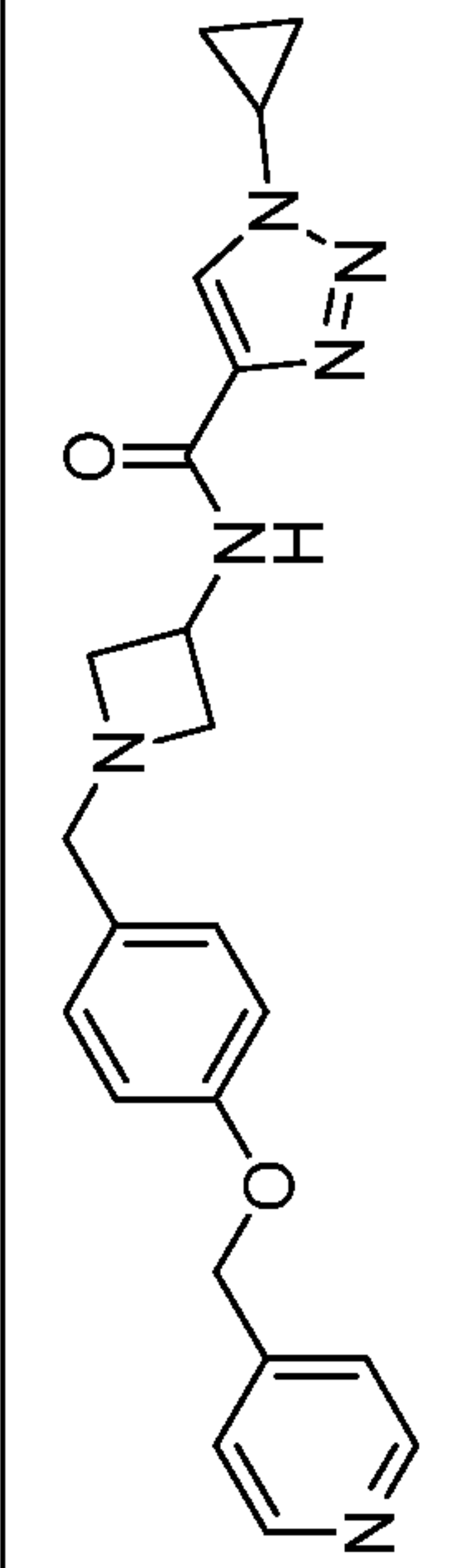
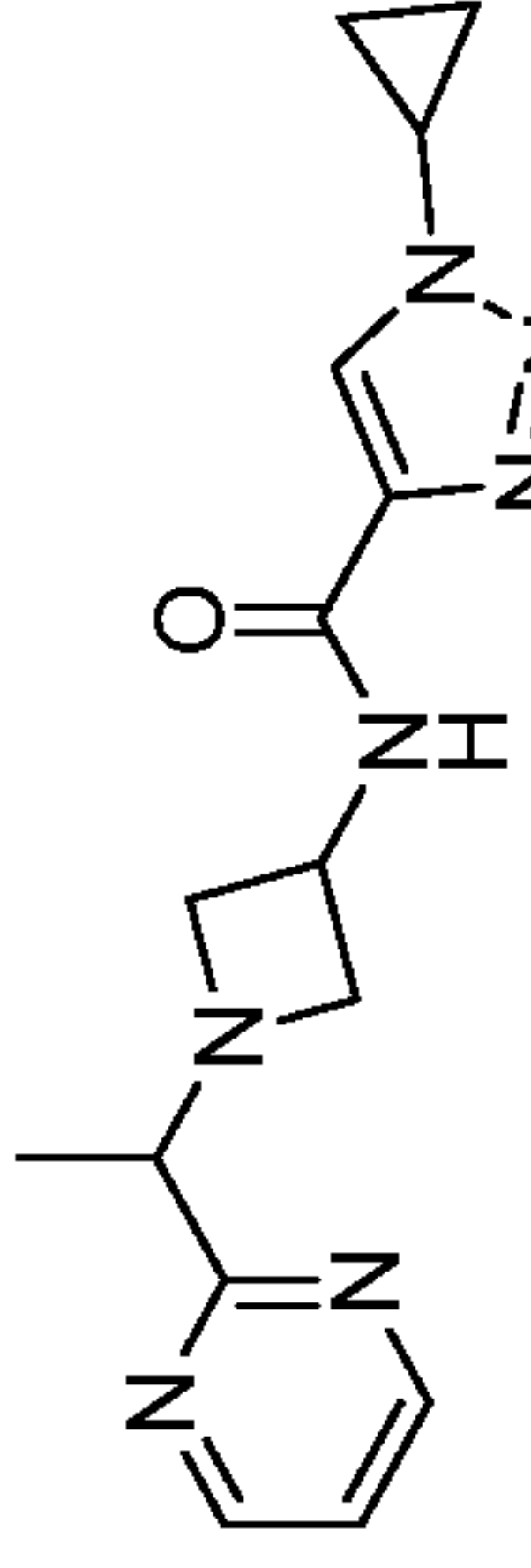
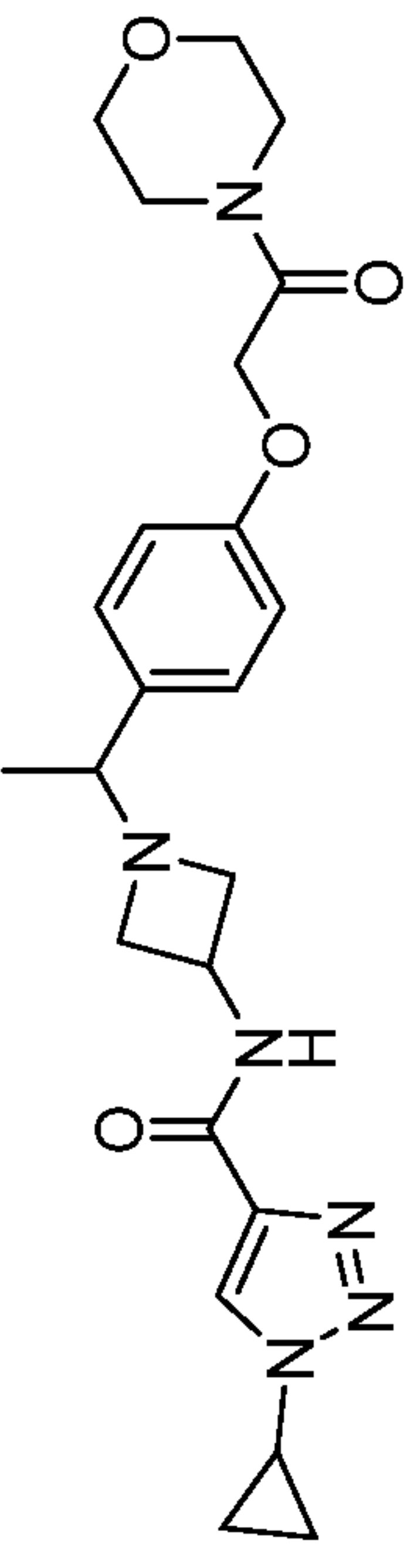
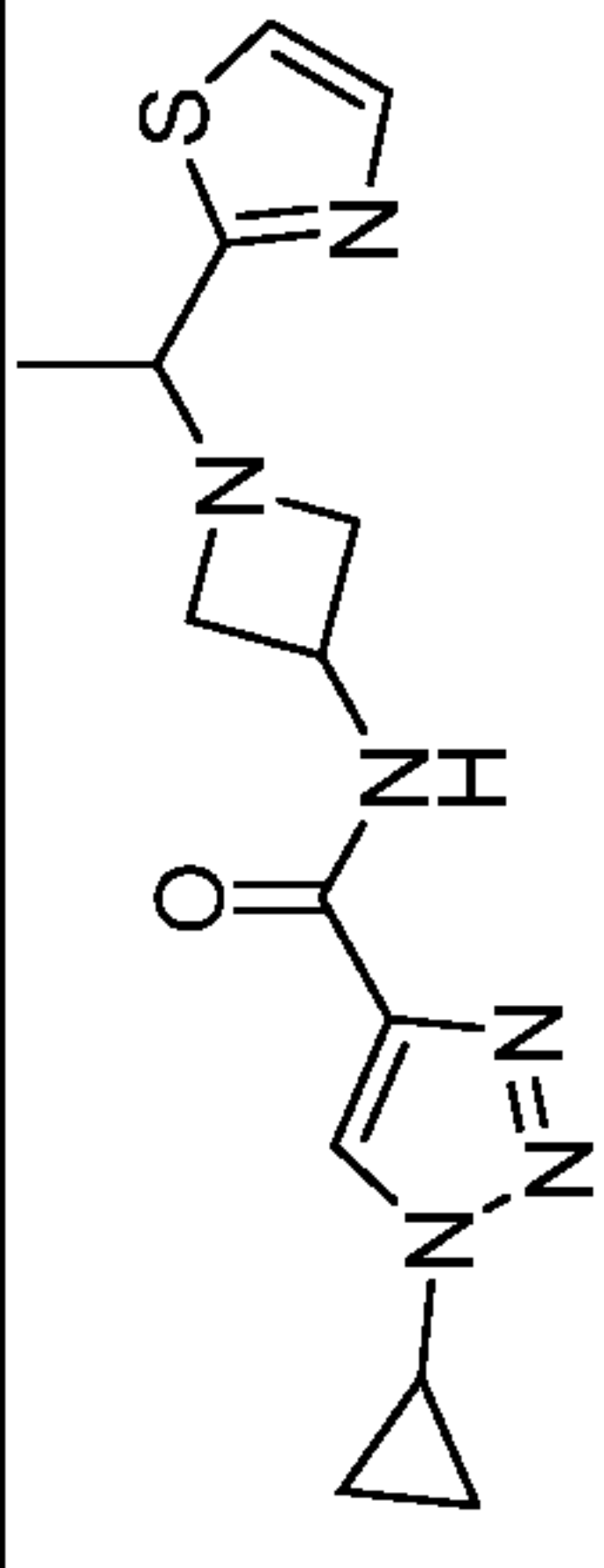
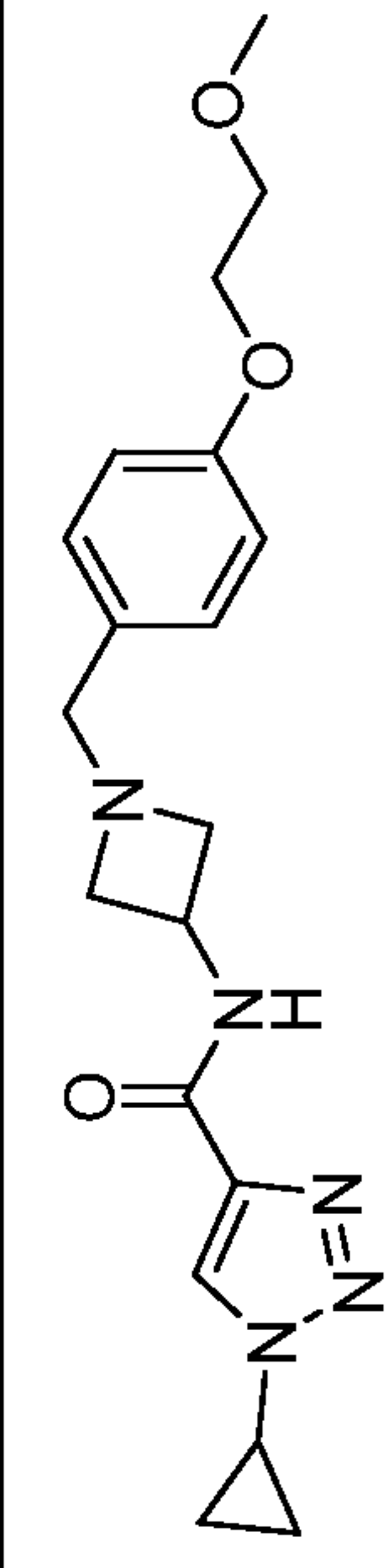
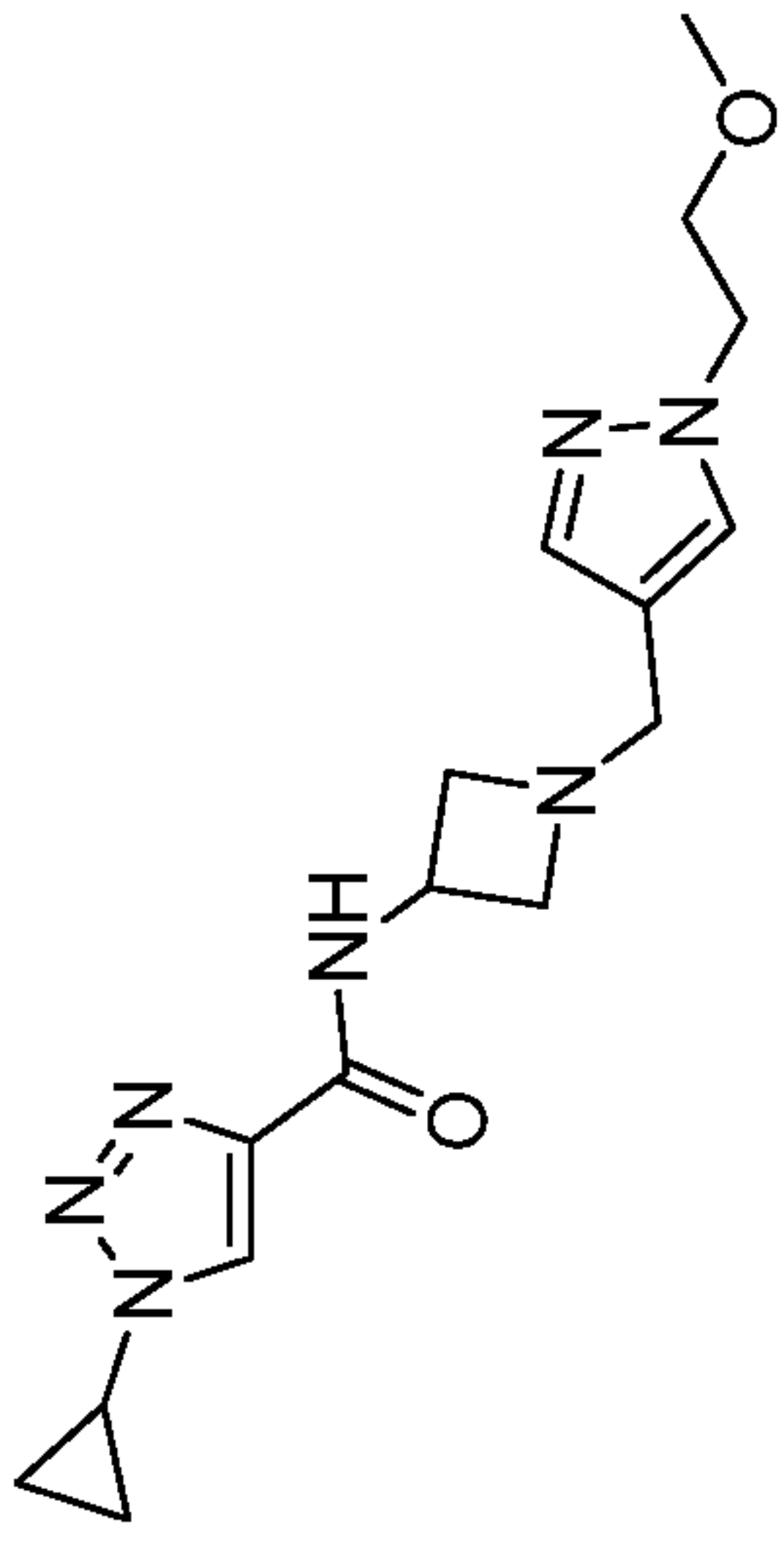
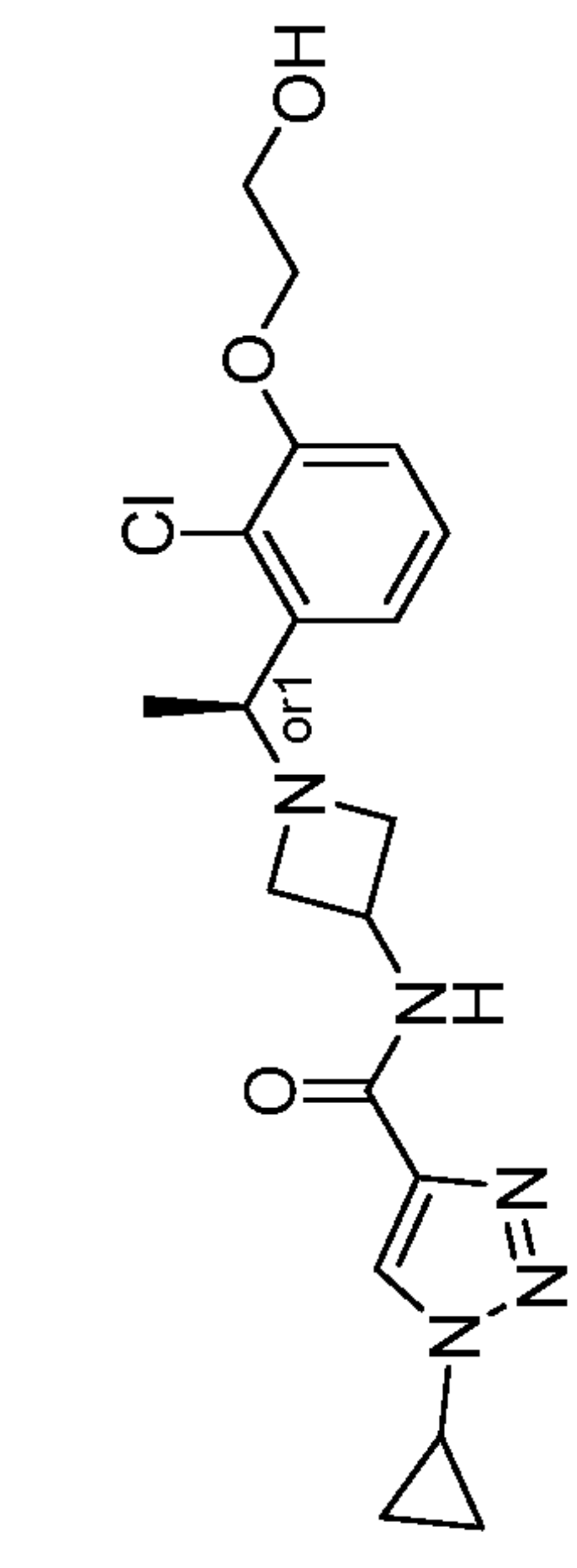
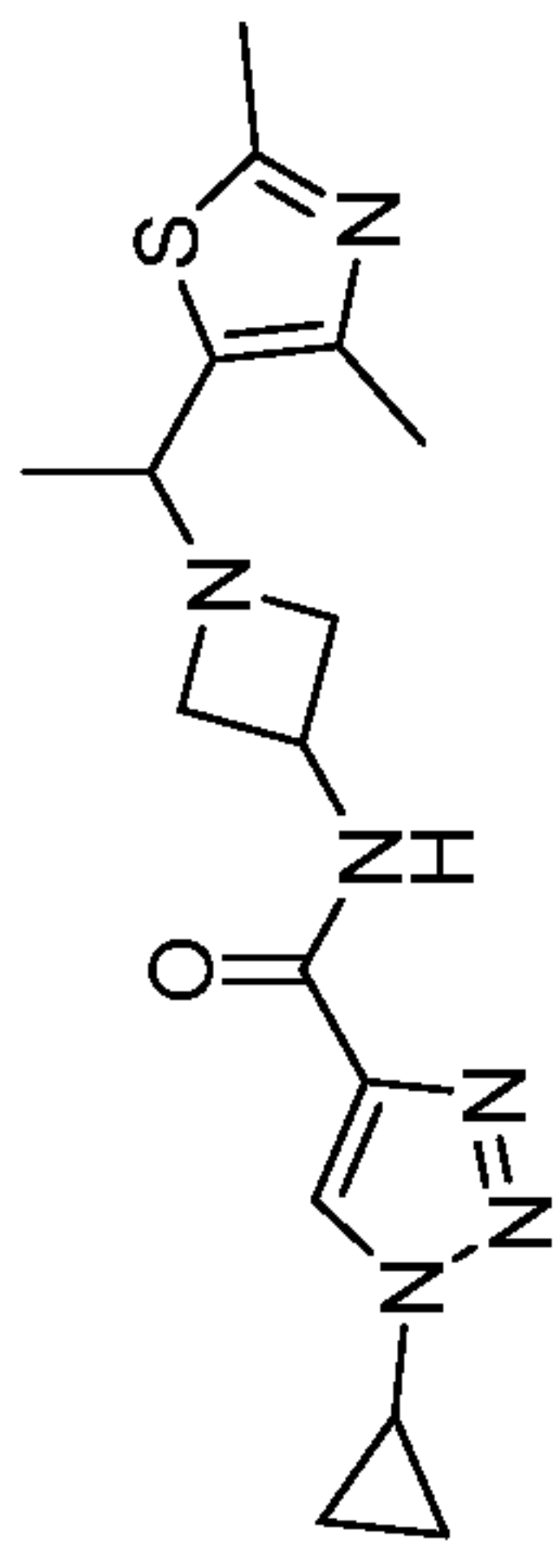
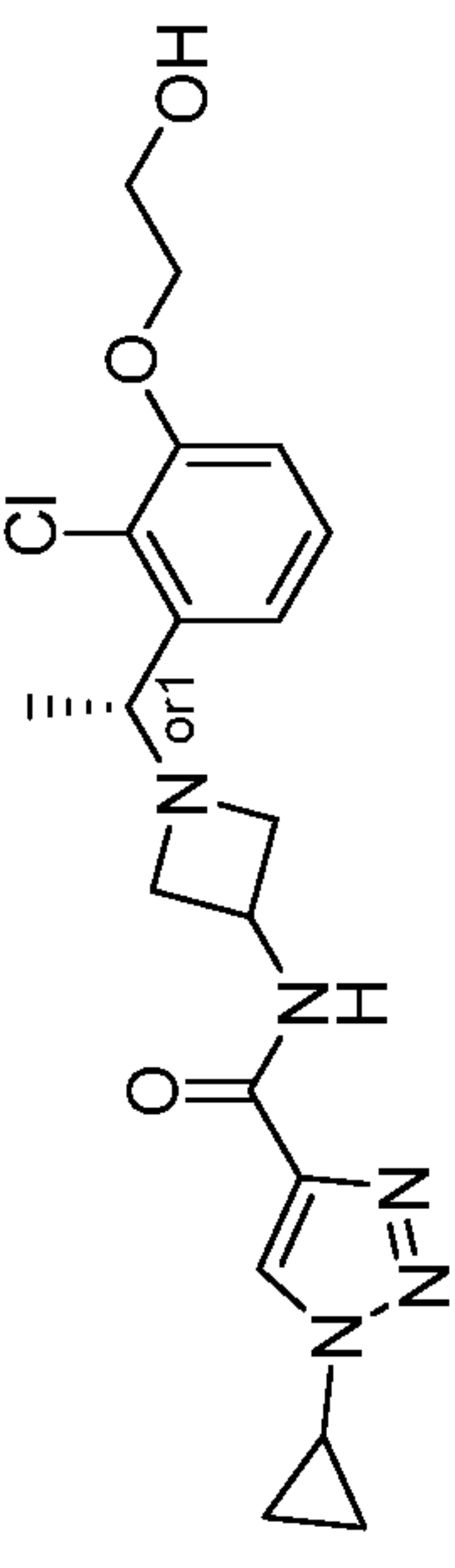
None		806	None		692
None		807	None		693
None		808	None		694
None		809	None		695

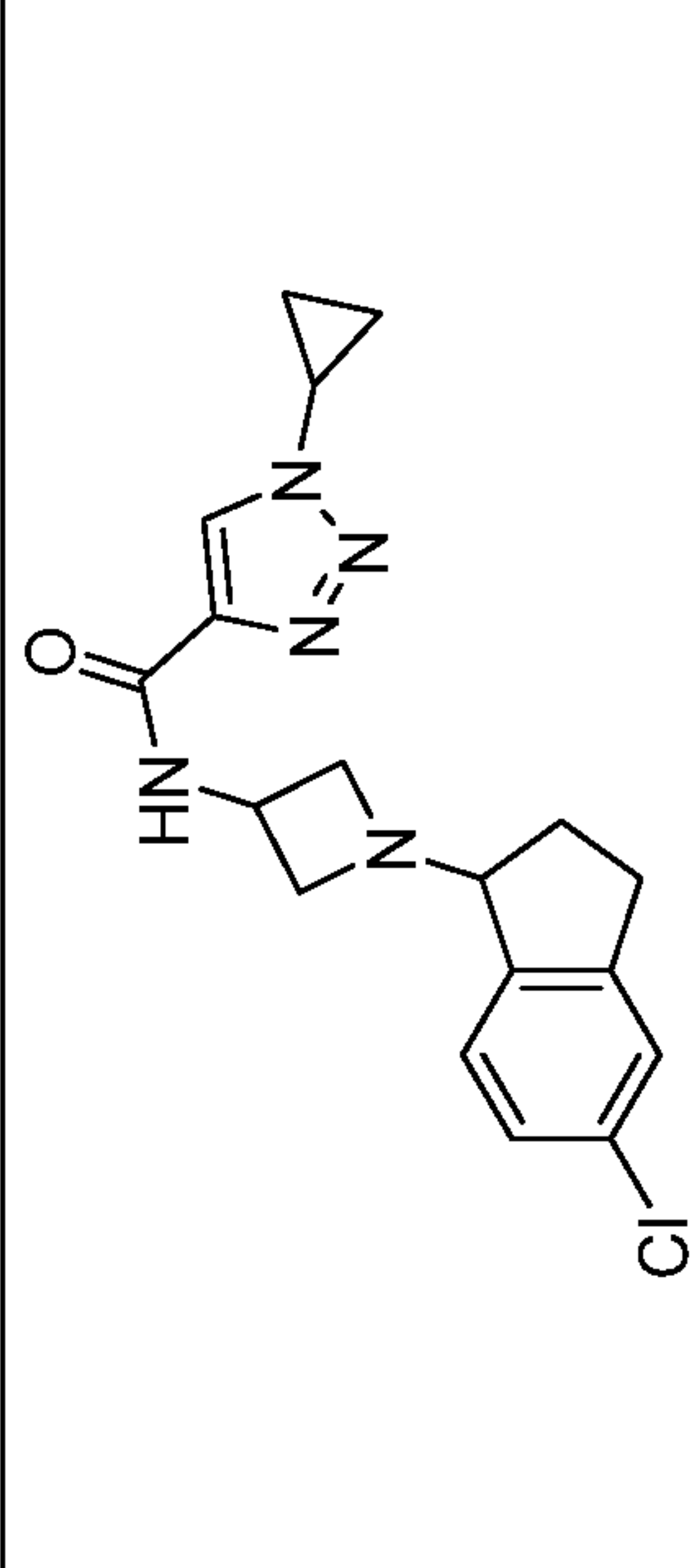
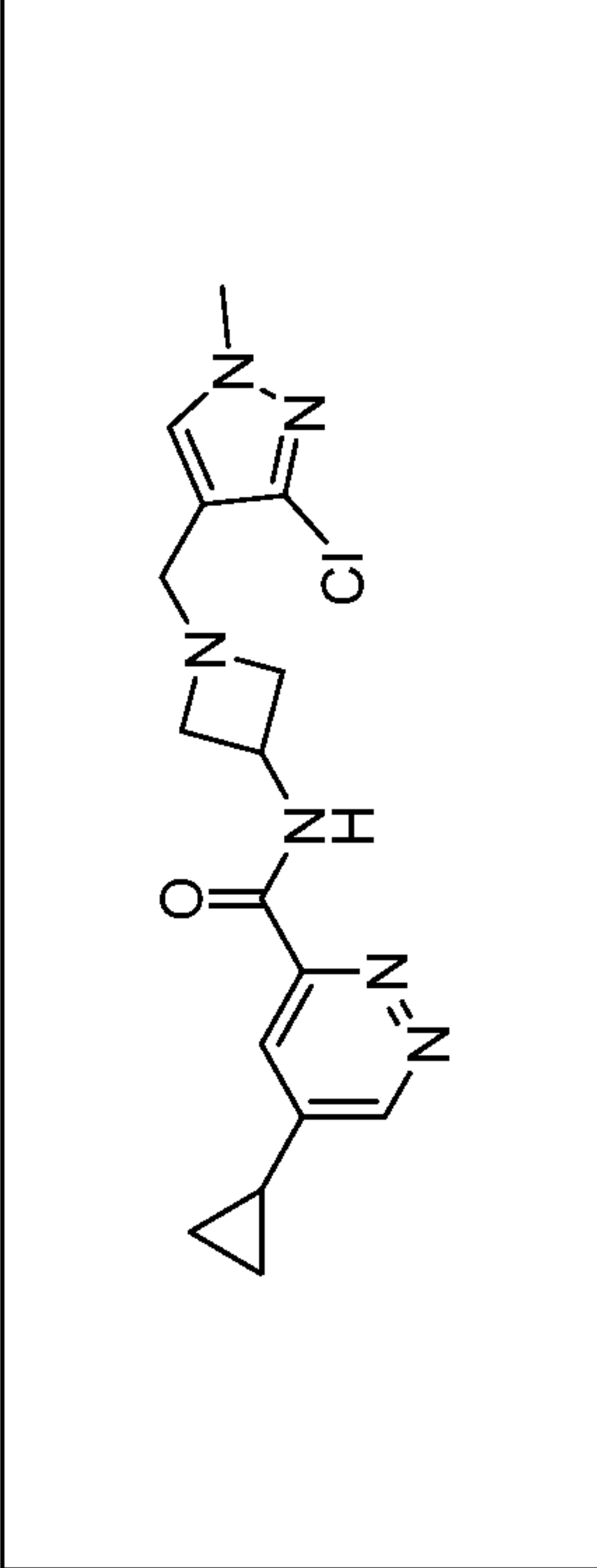
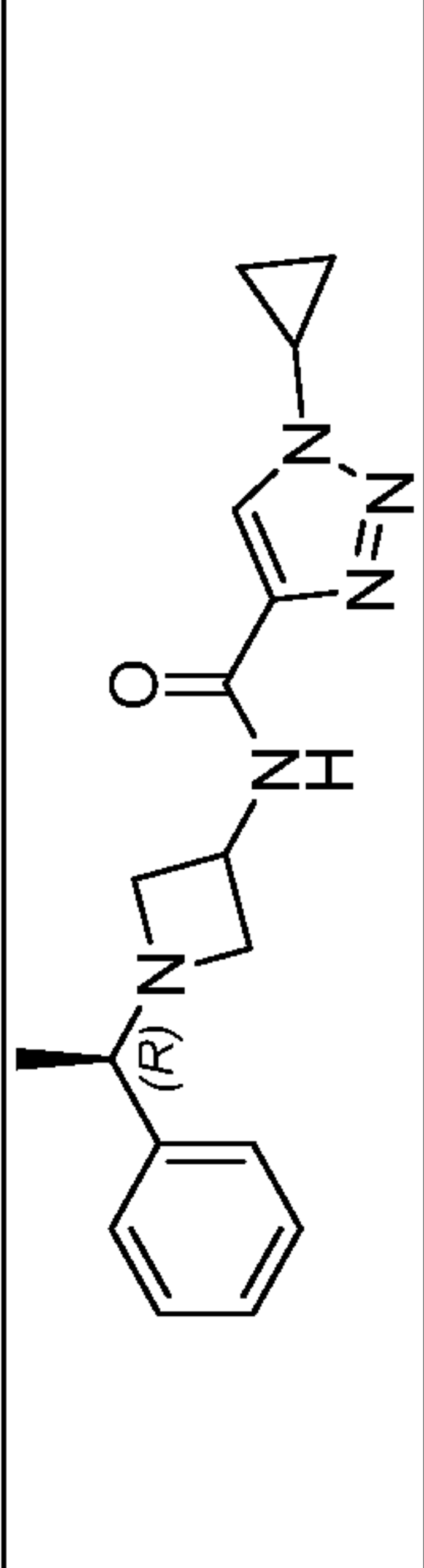
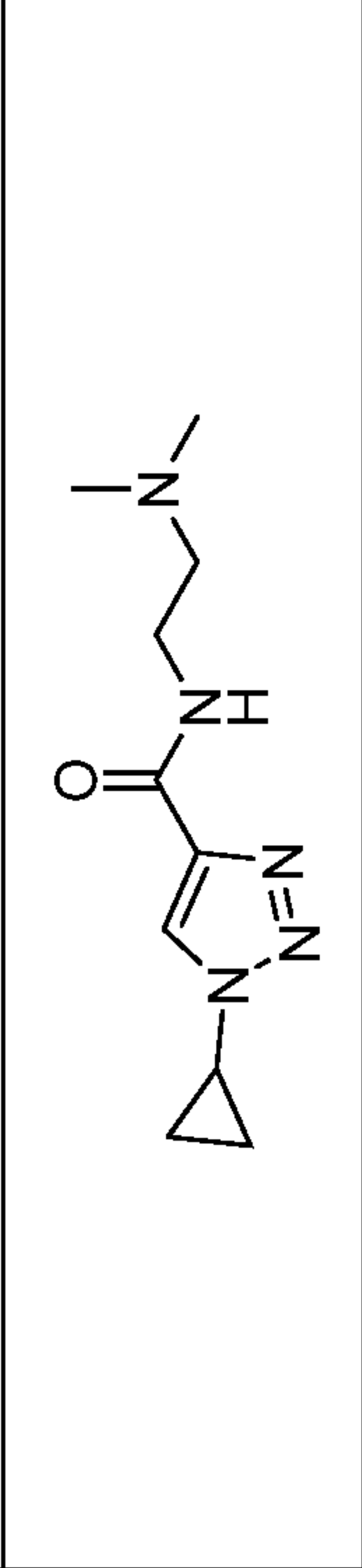
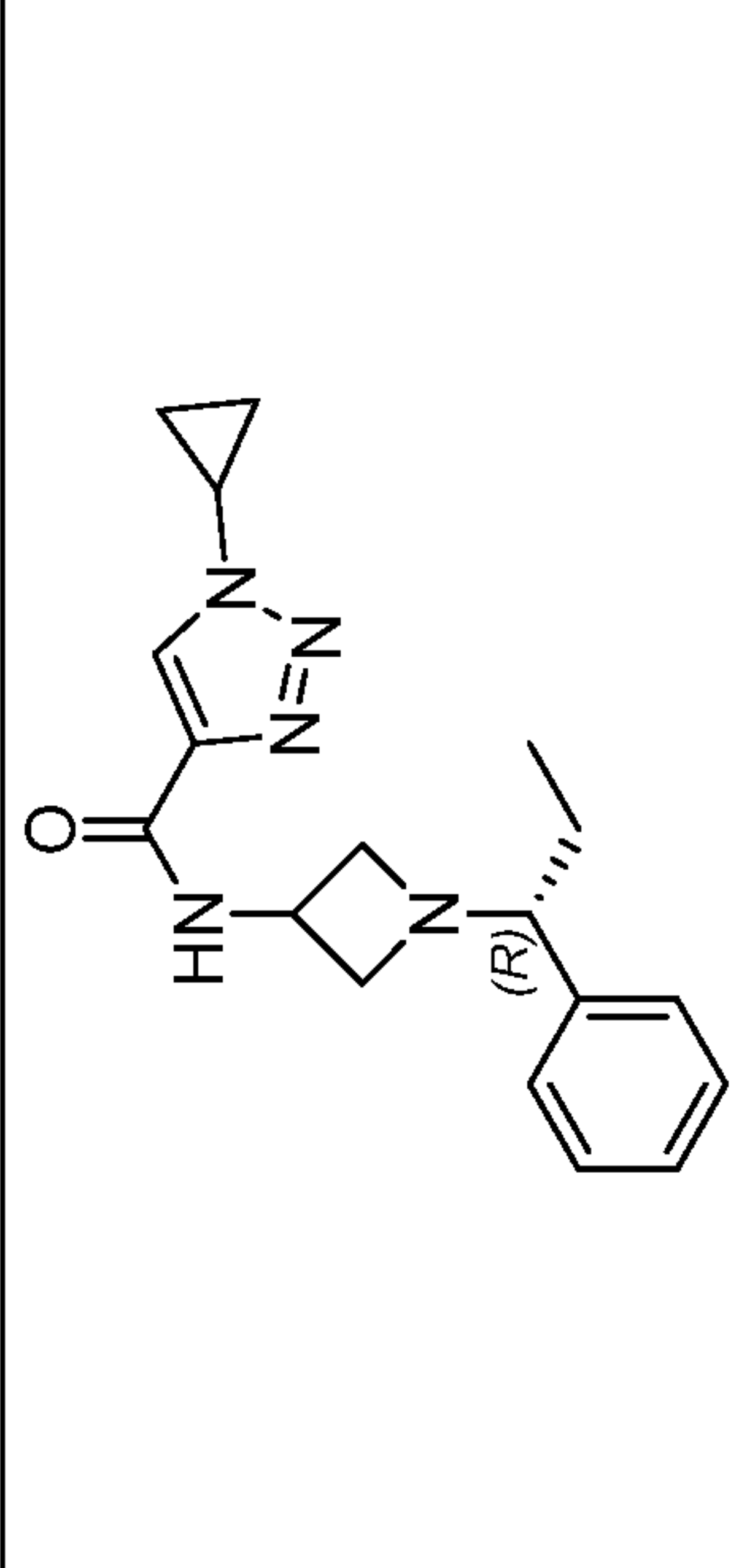
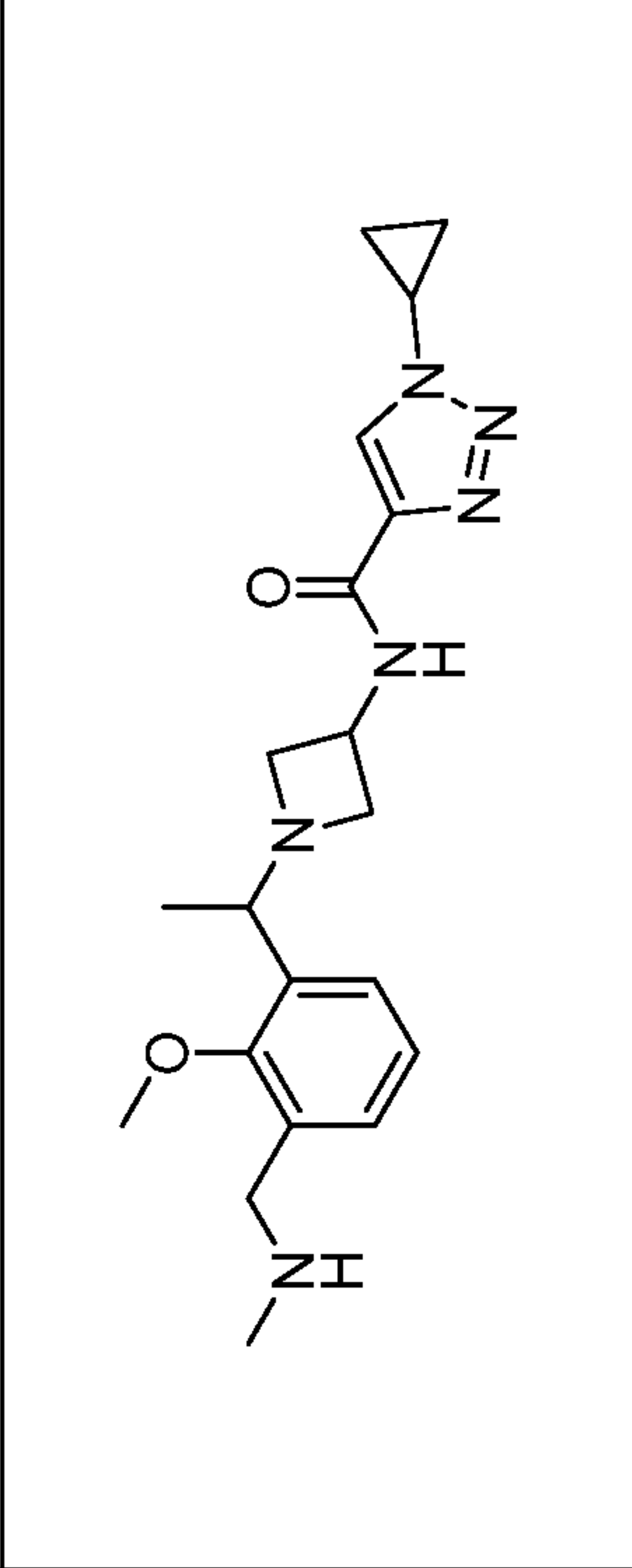
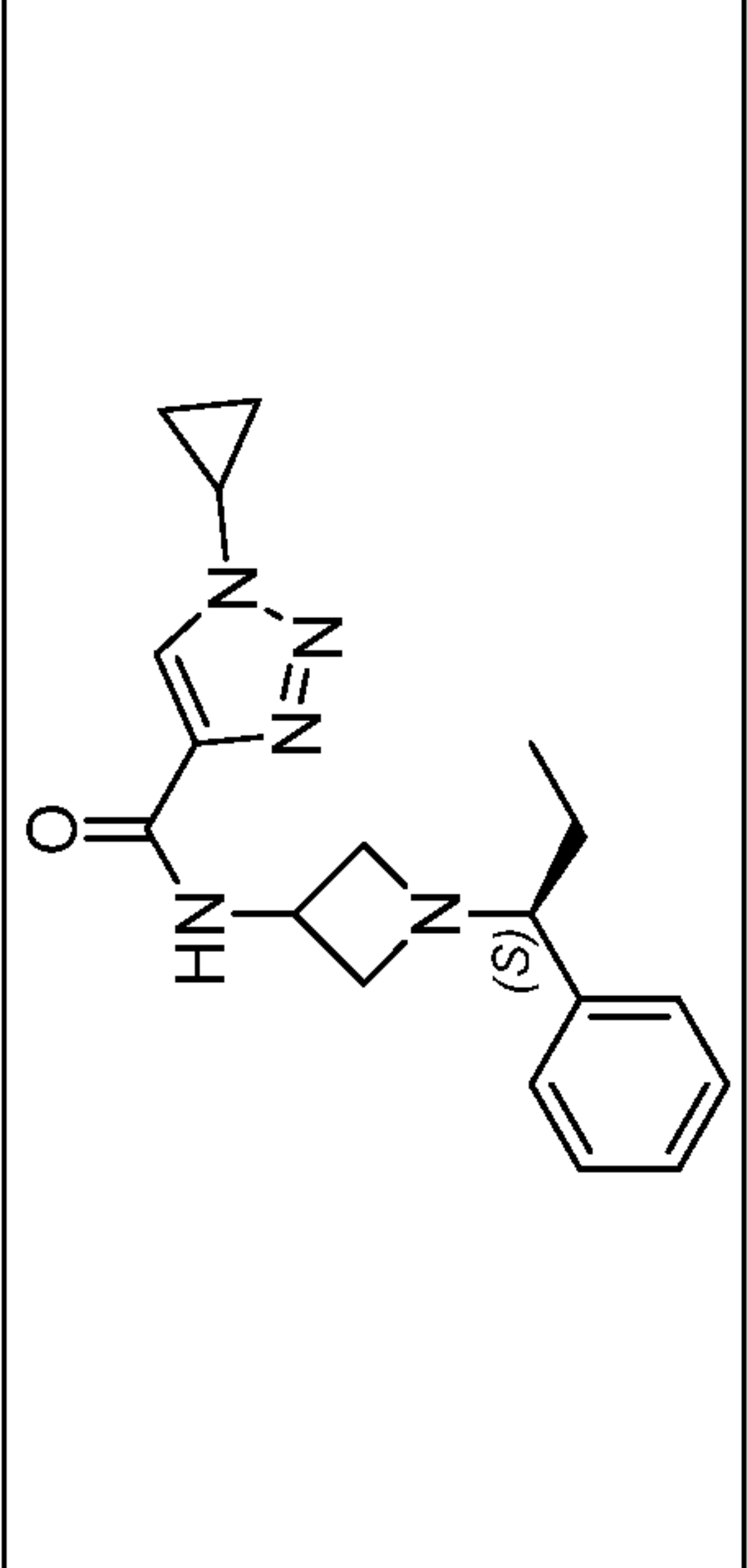
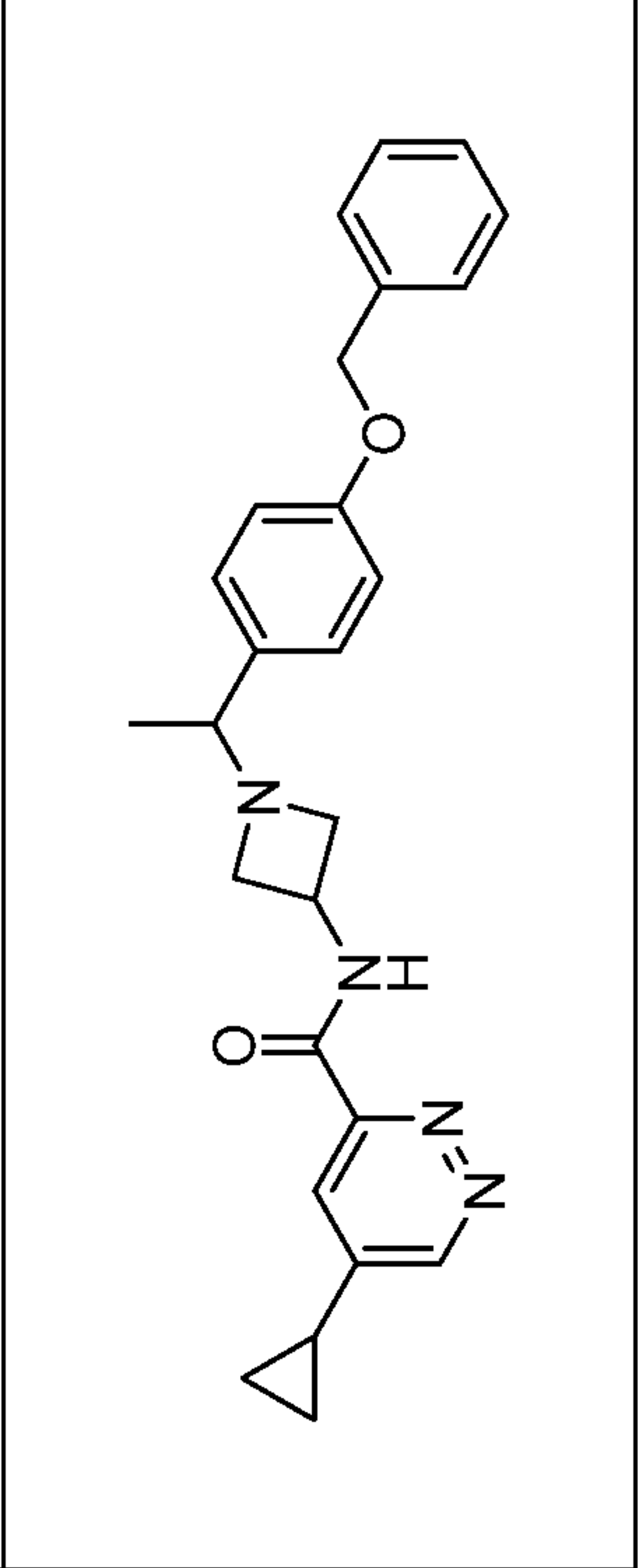
696		None	810		None
697		None	811		None
698		None	812		None
699		None	813		None

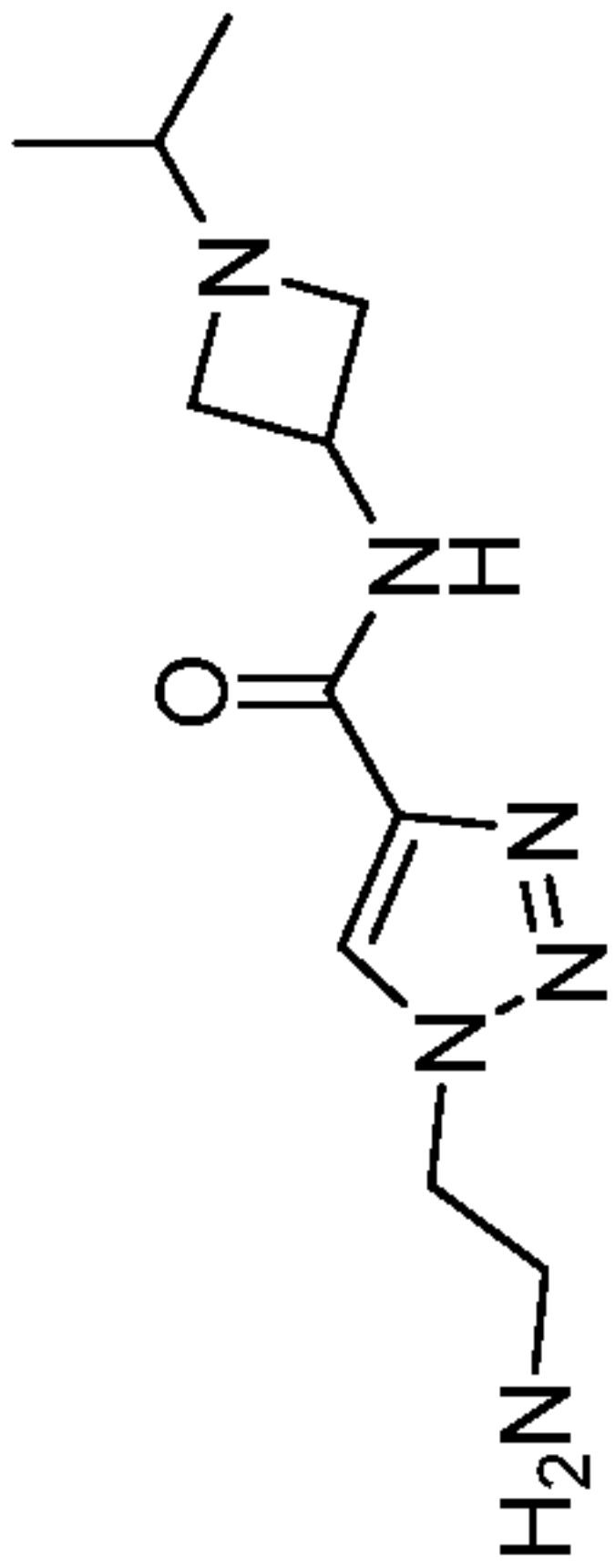
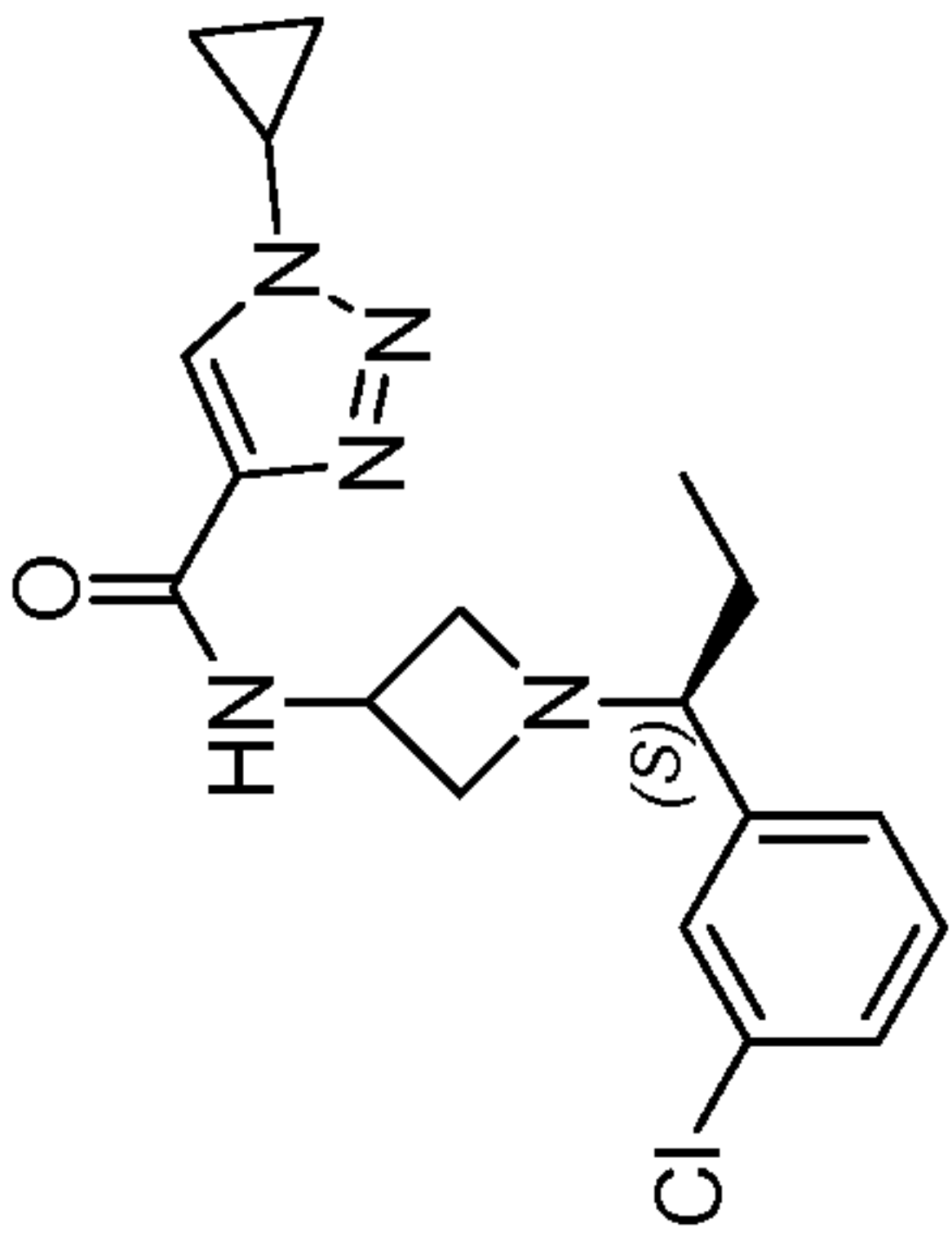
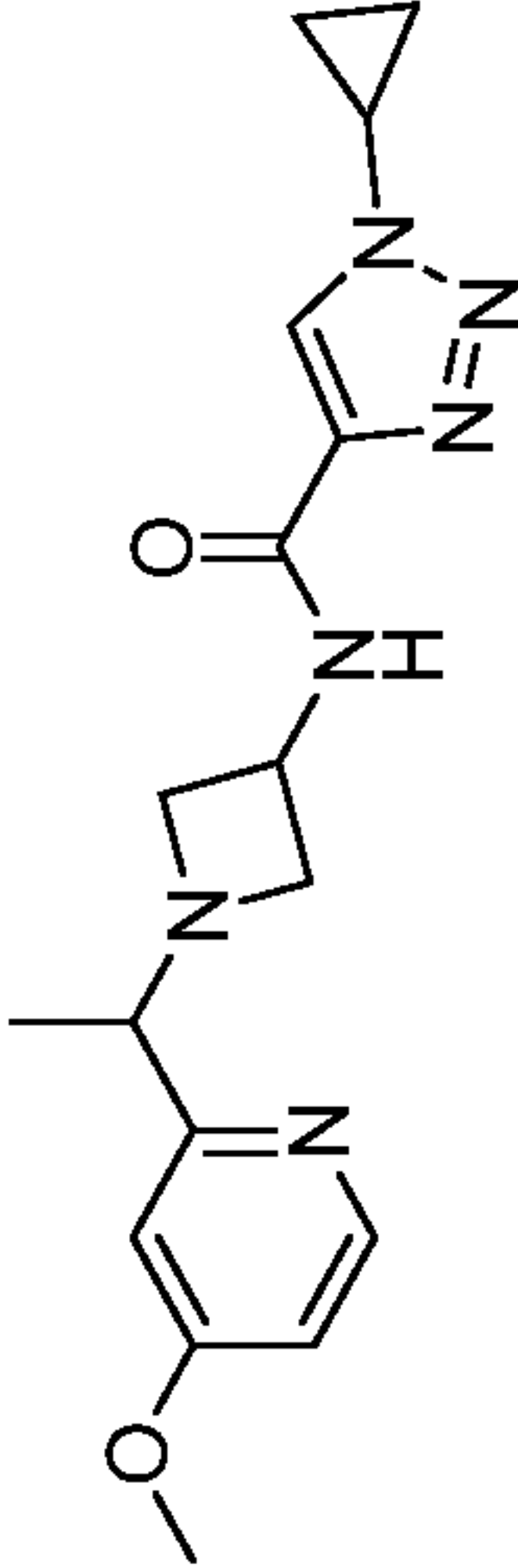
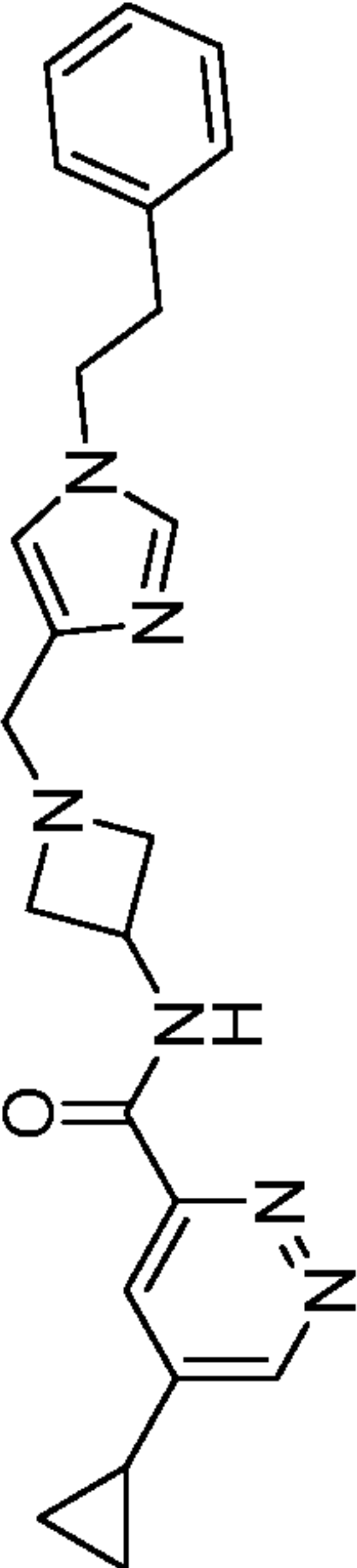
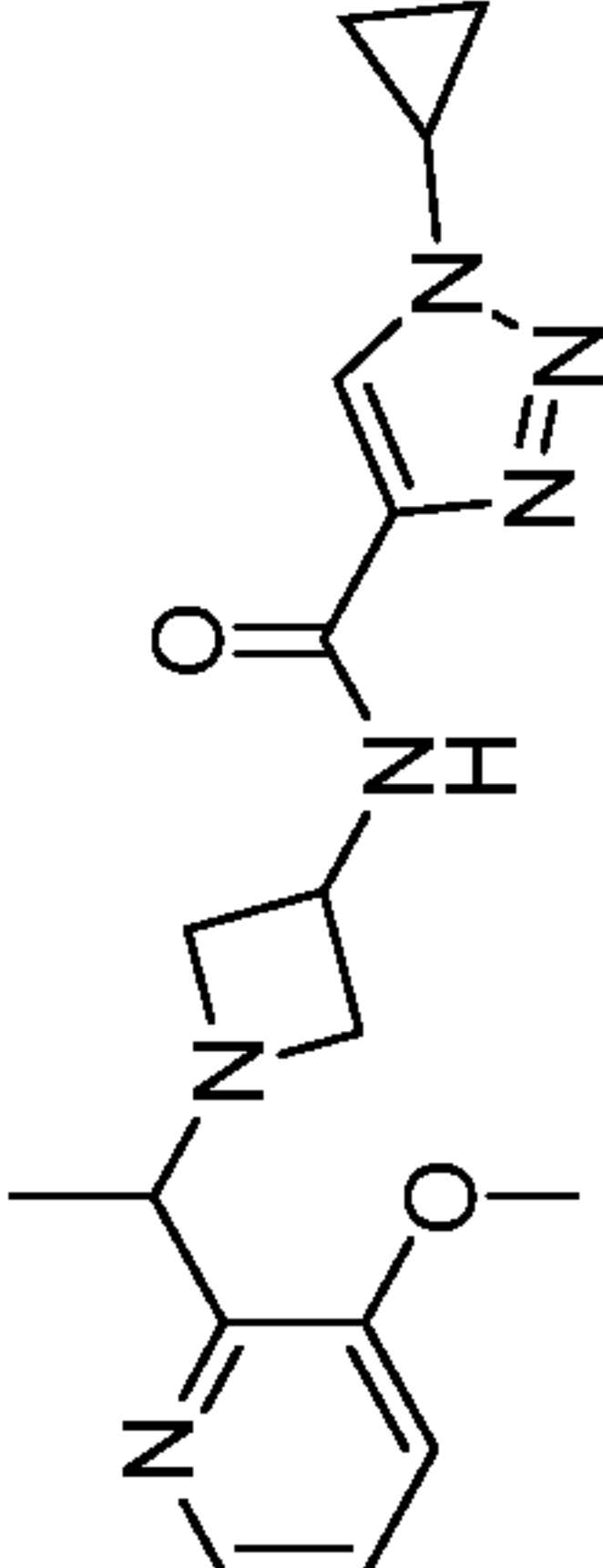
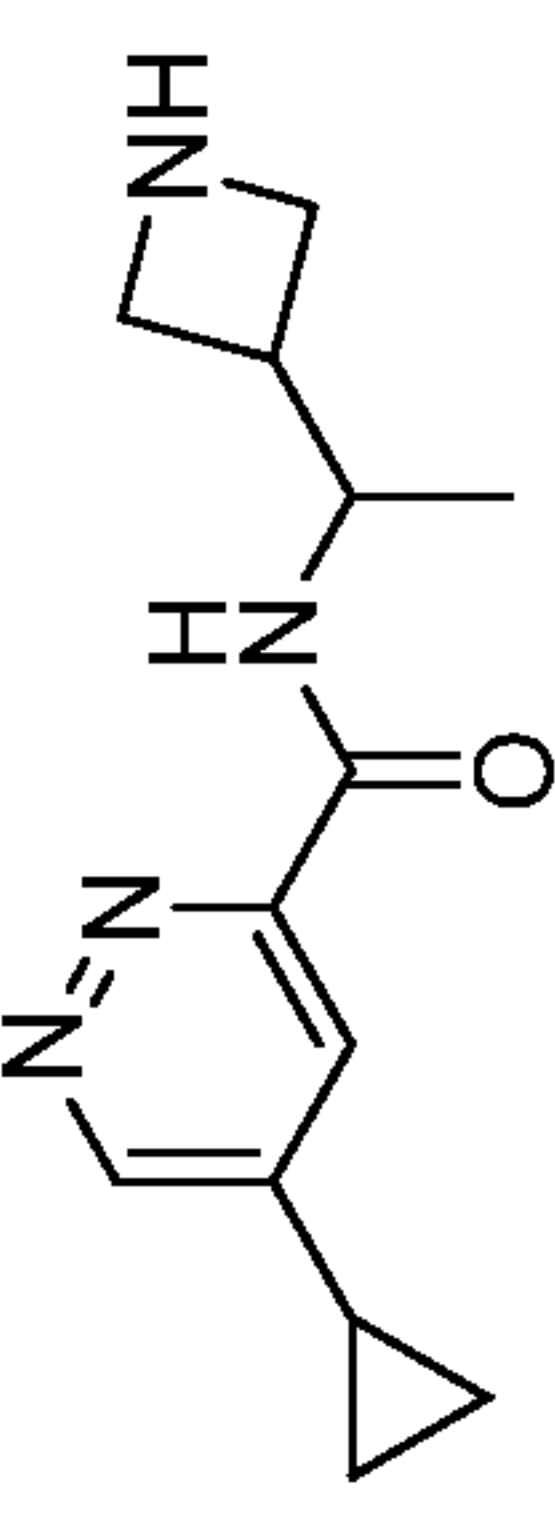
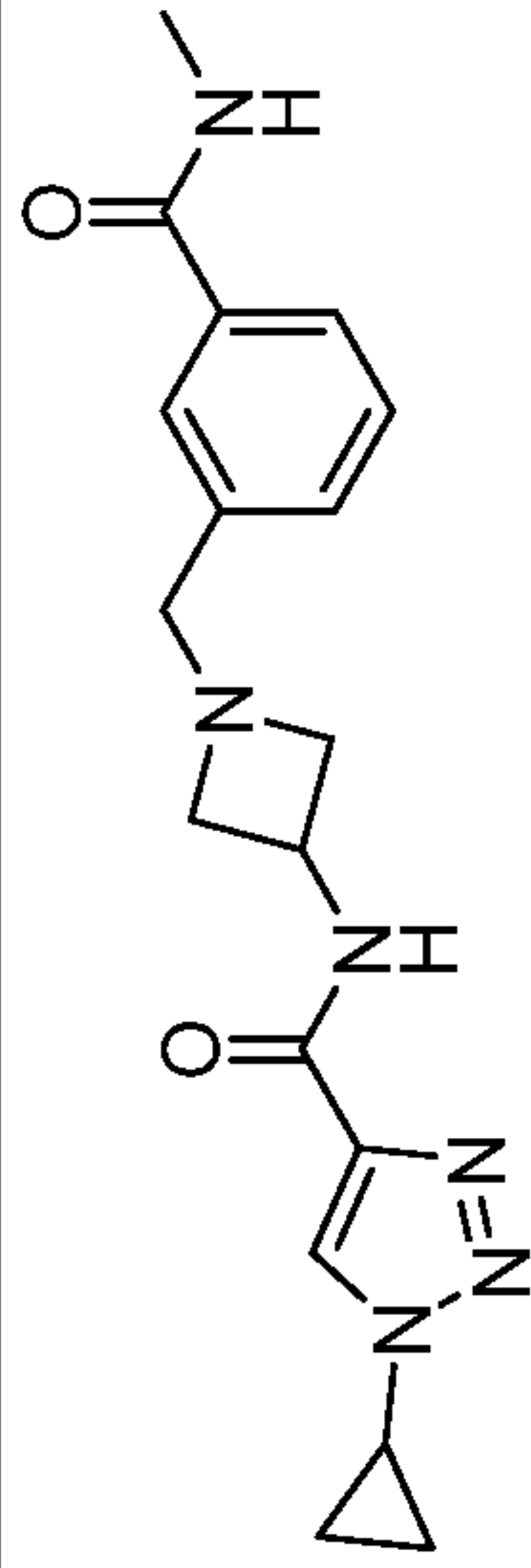
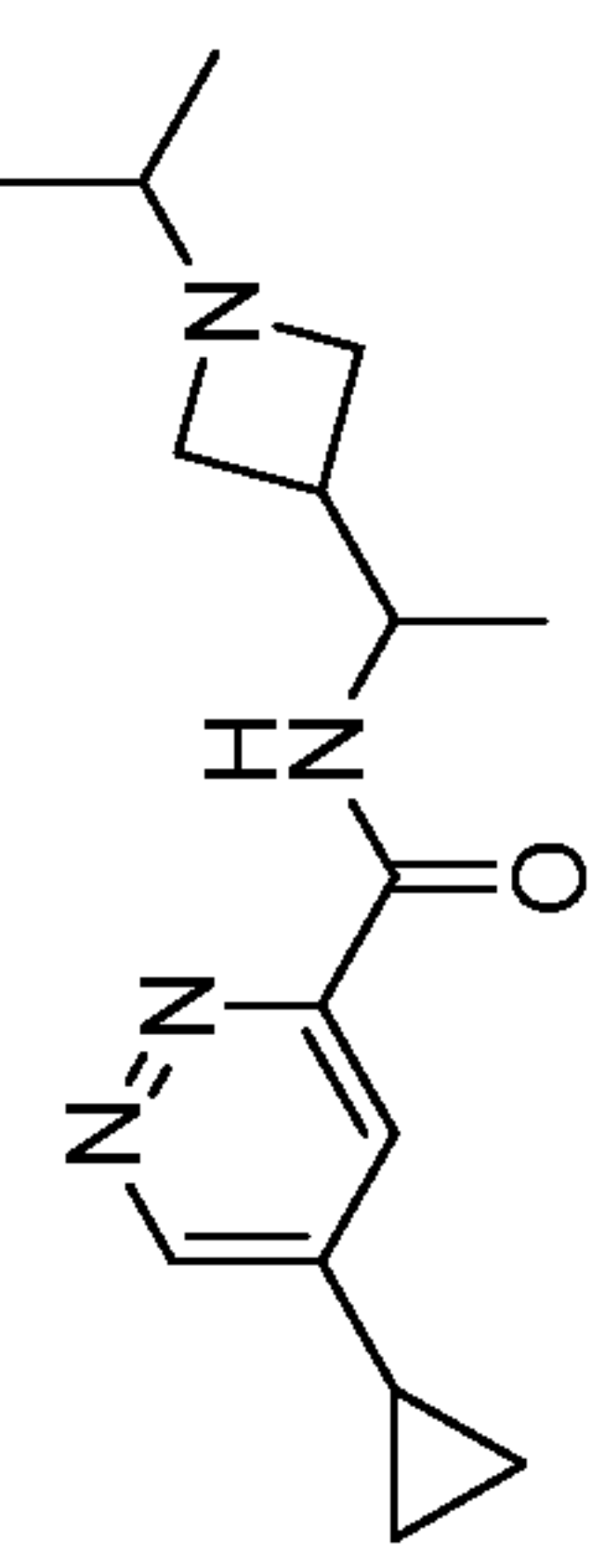
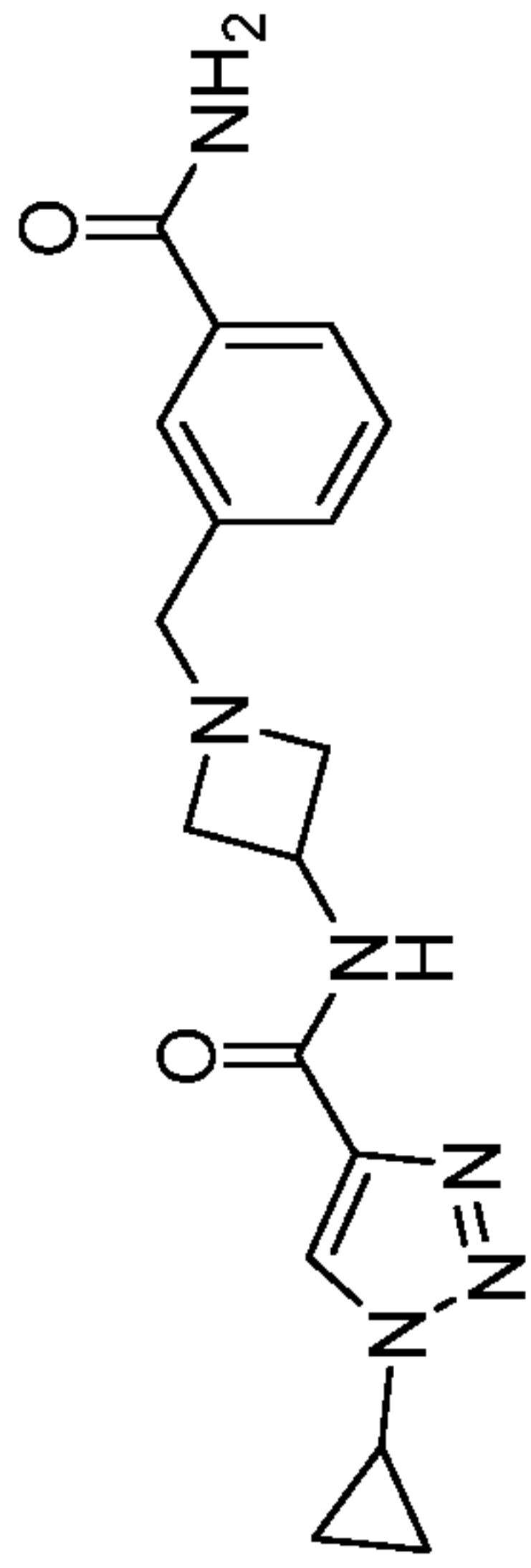
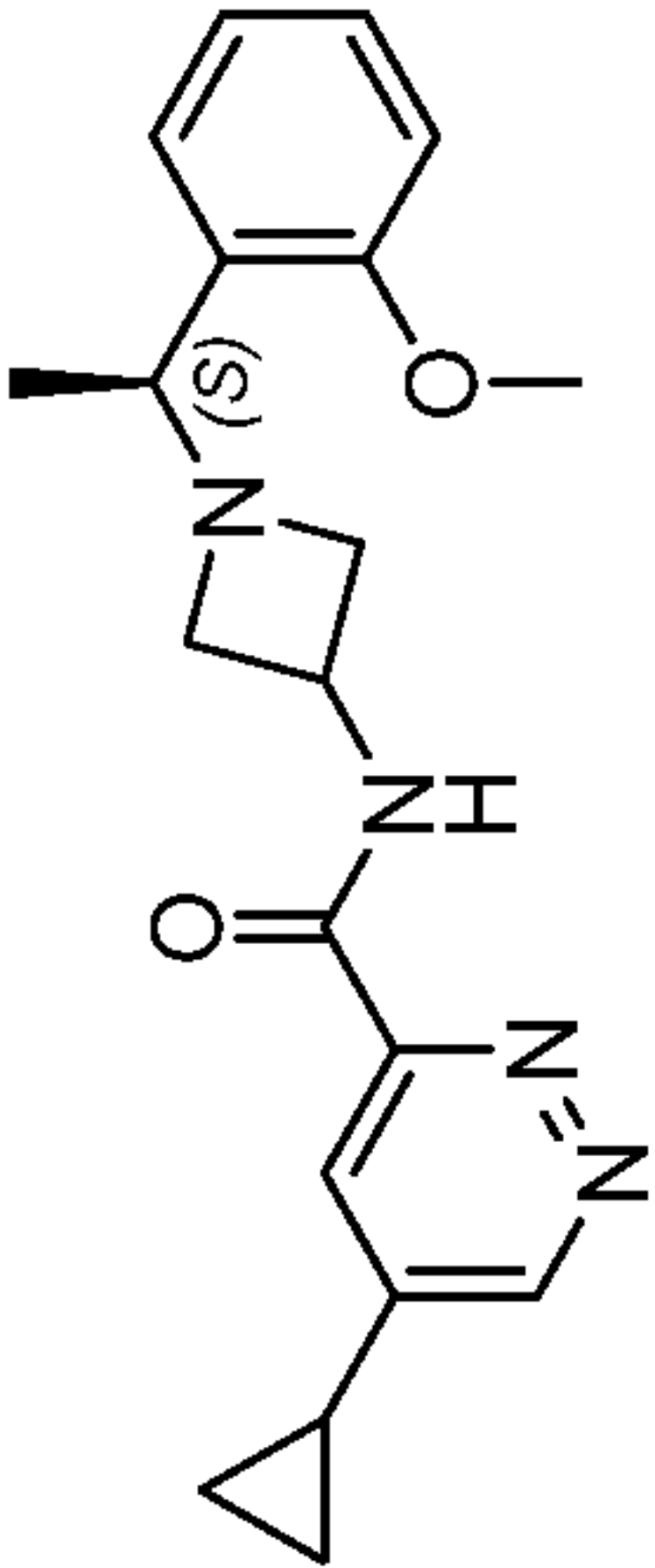
700		None	814		None
701		None	815		None
702		None	816		None
703		None	817		None

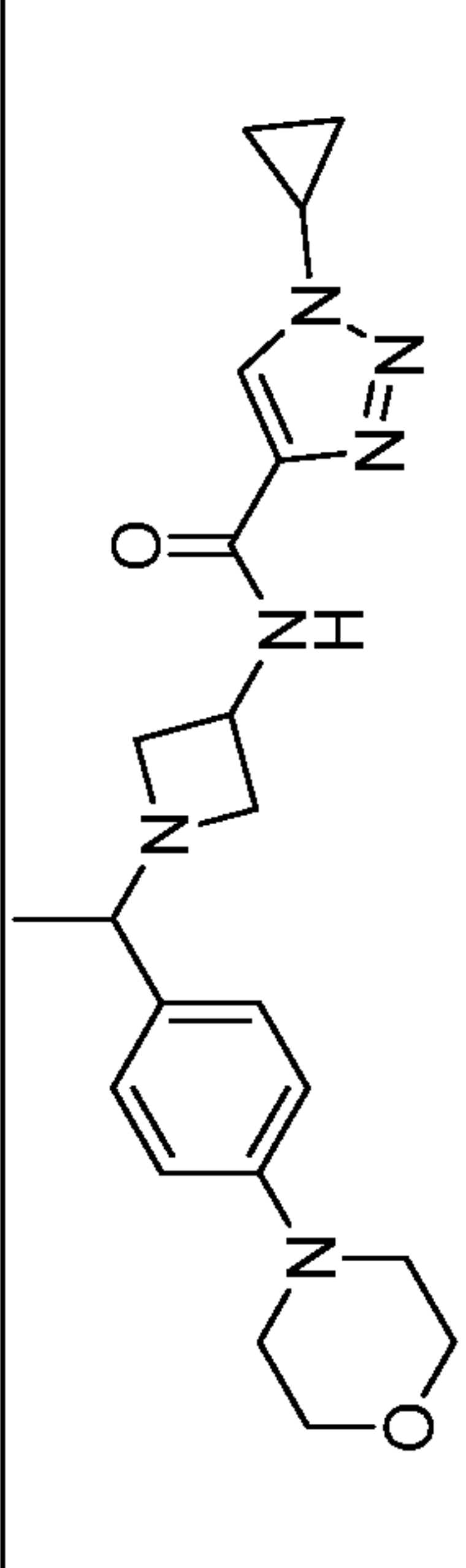
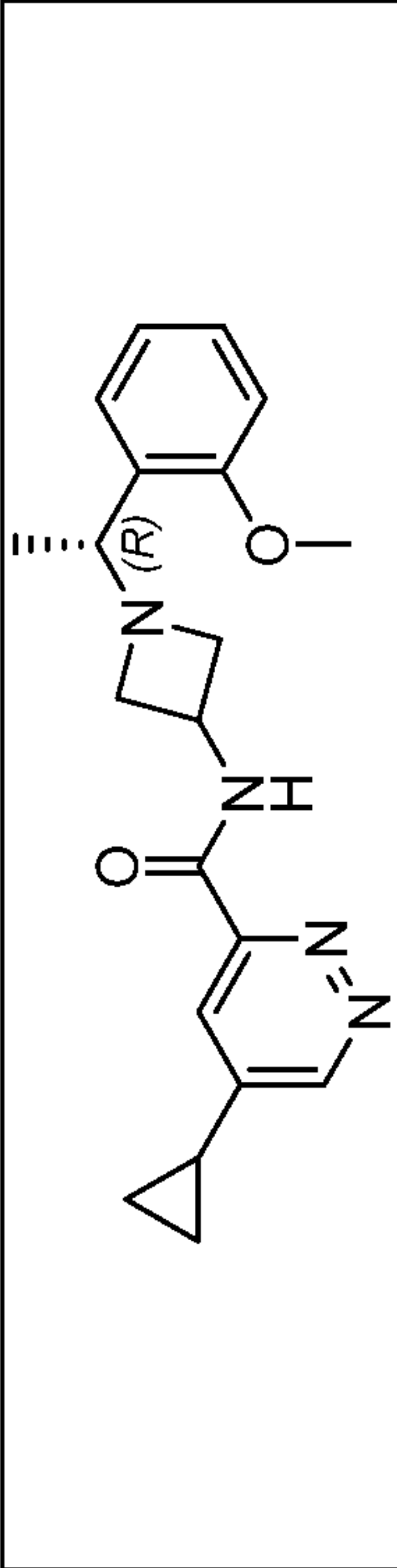
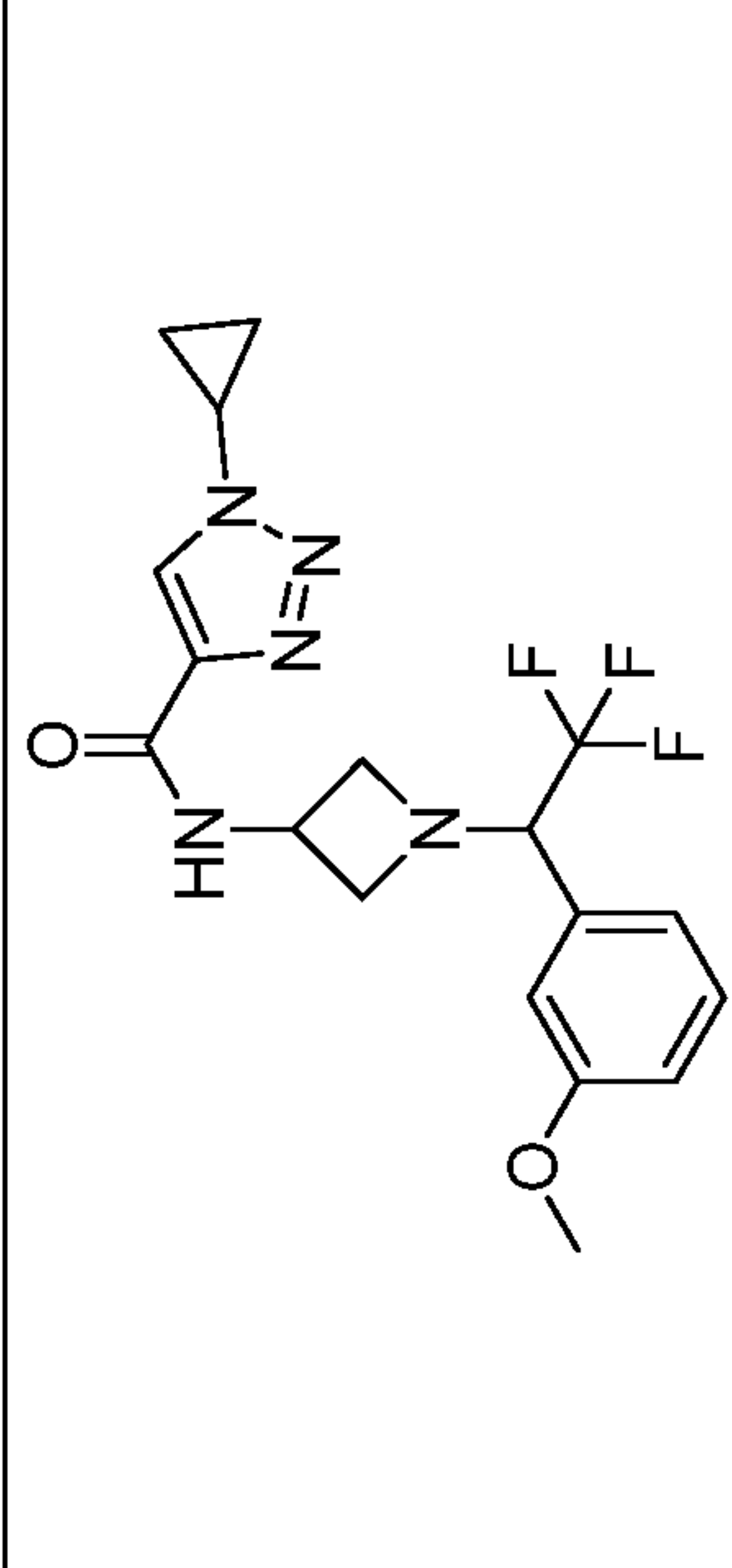
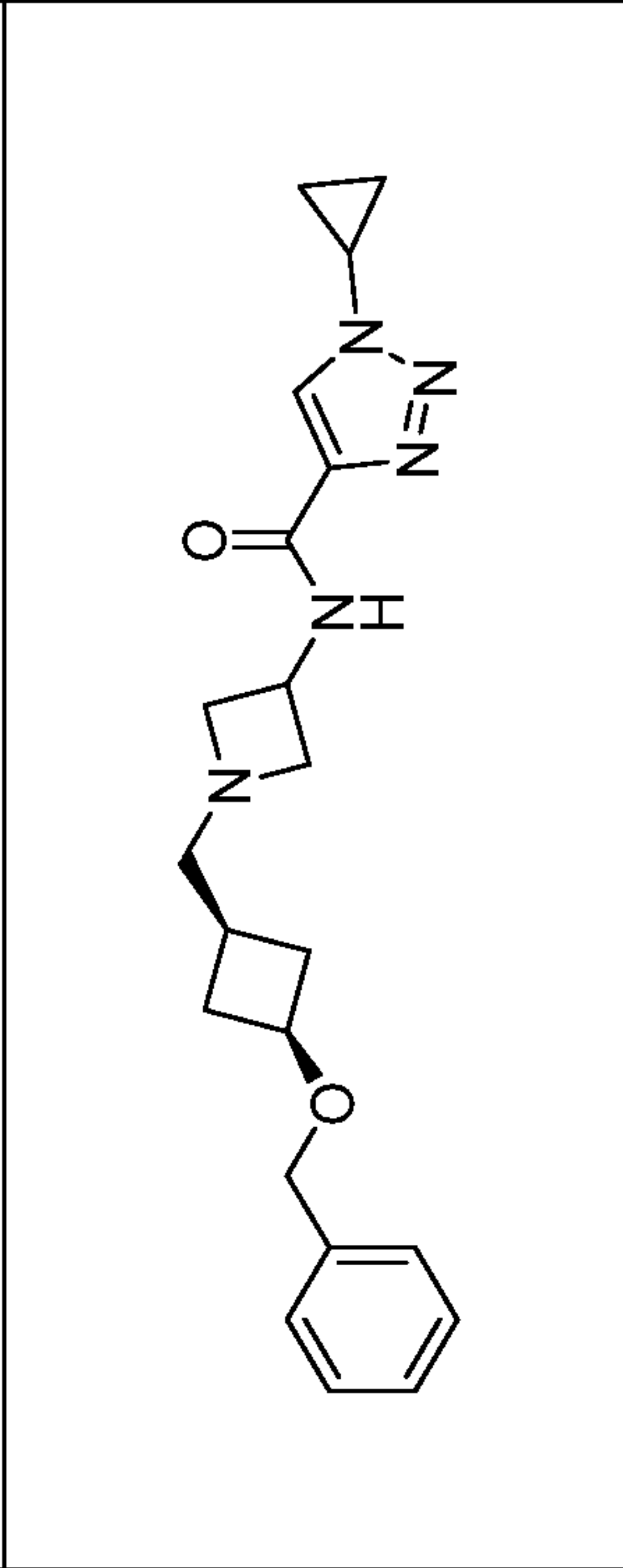
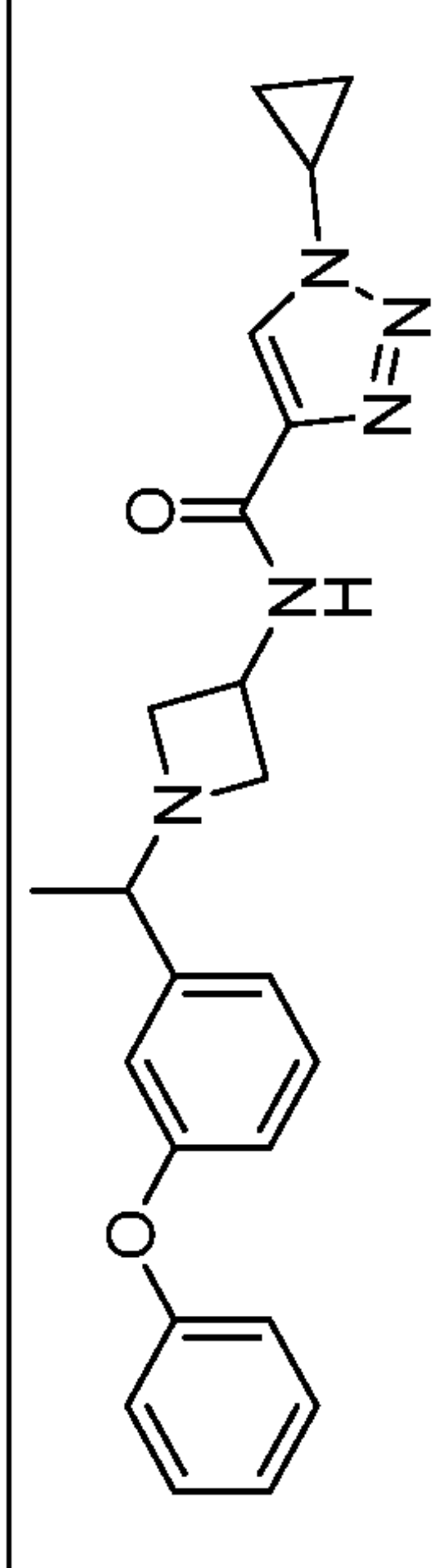
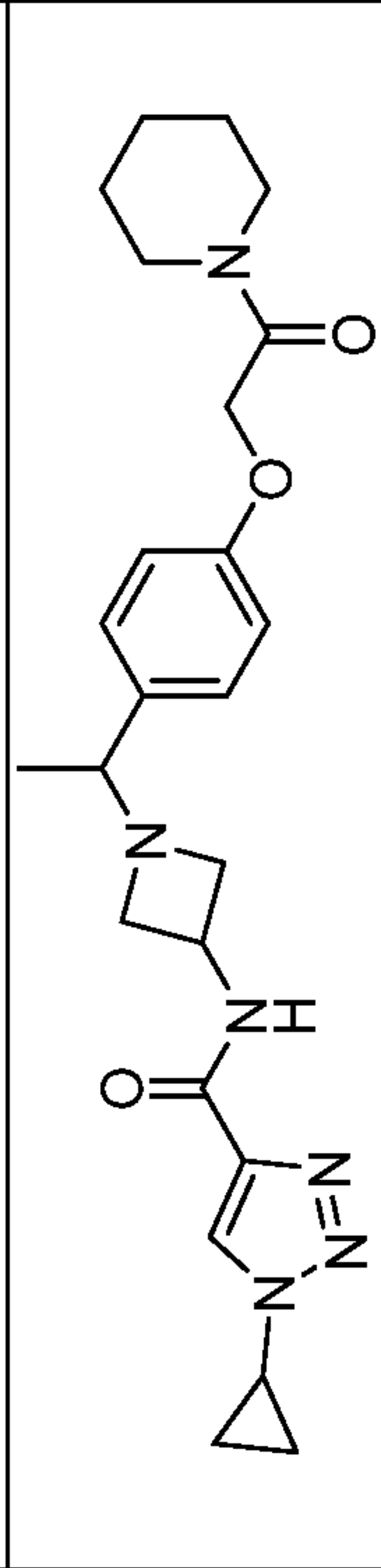
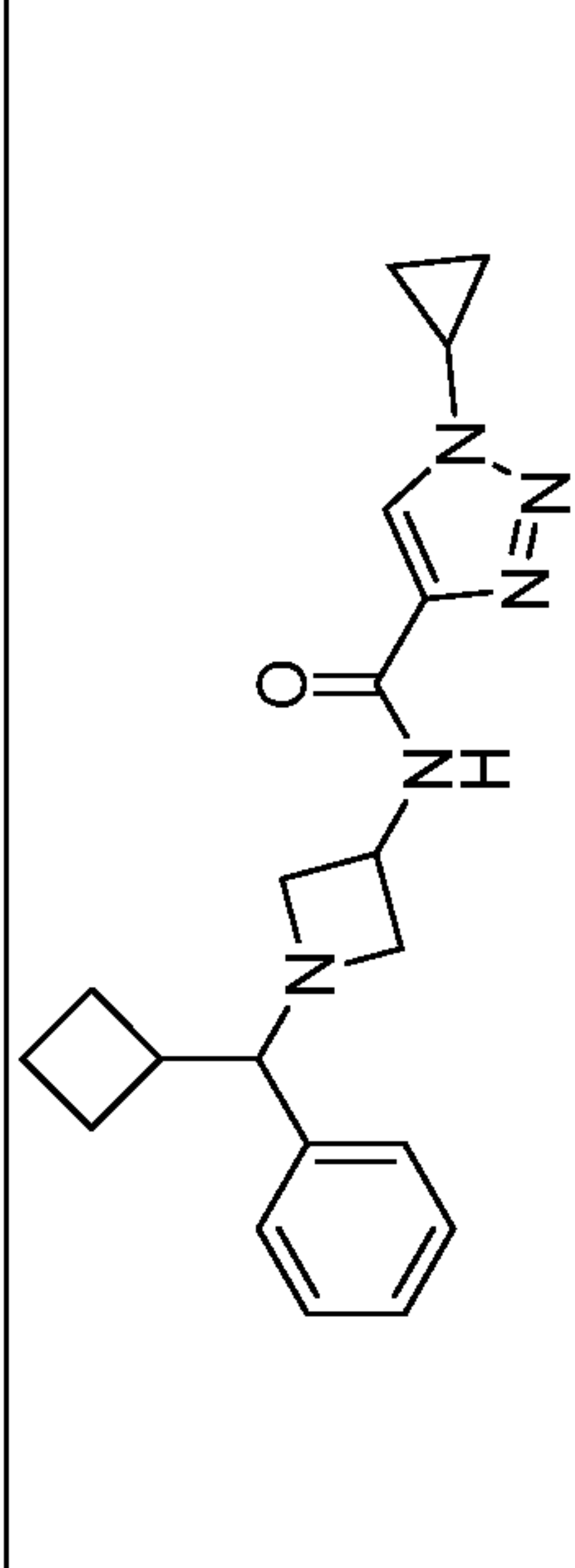
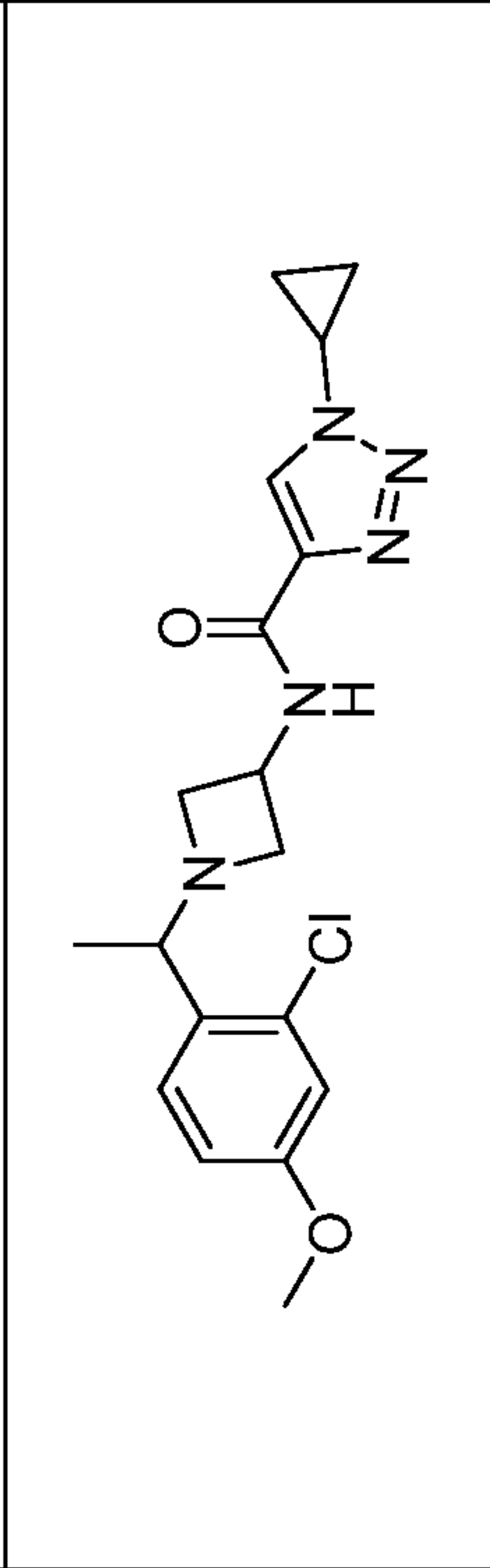
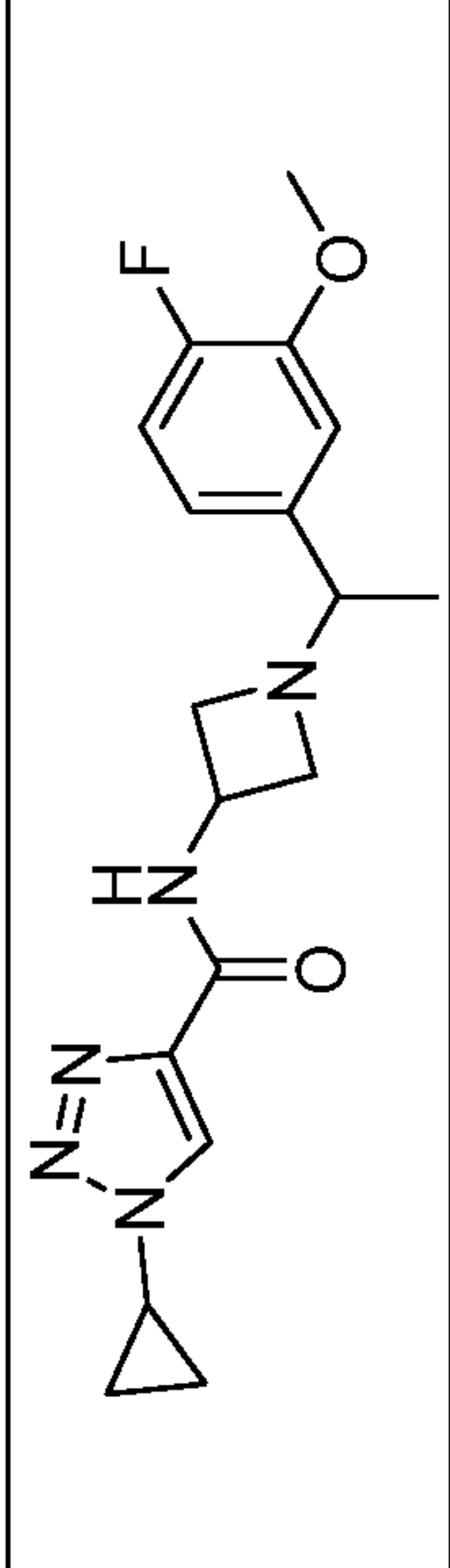
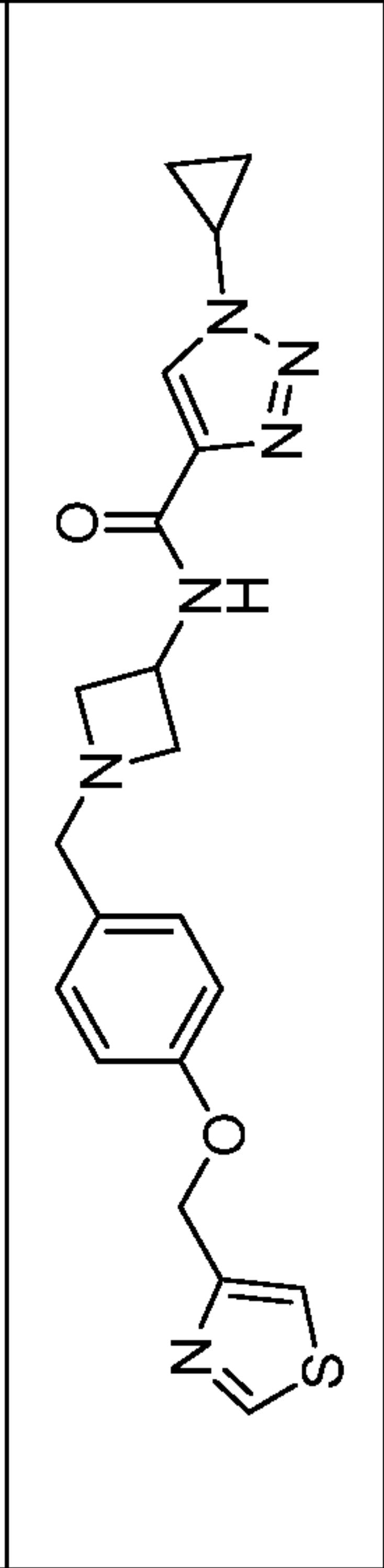
704		None	818		None
705		None	819		None
706		None	820		None
707		None	821		None
708		None	822		None
709		None	823		None

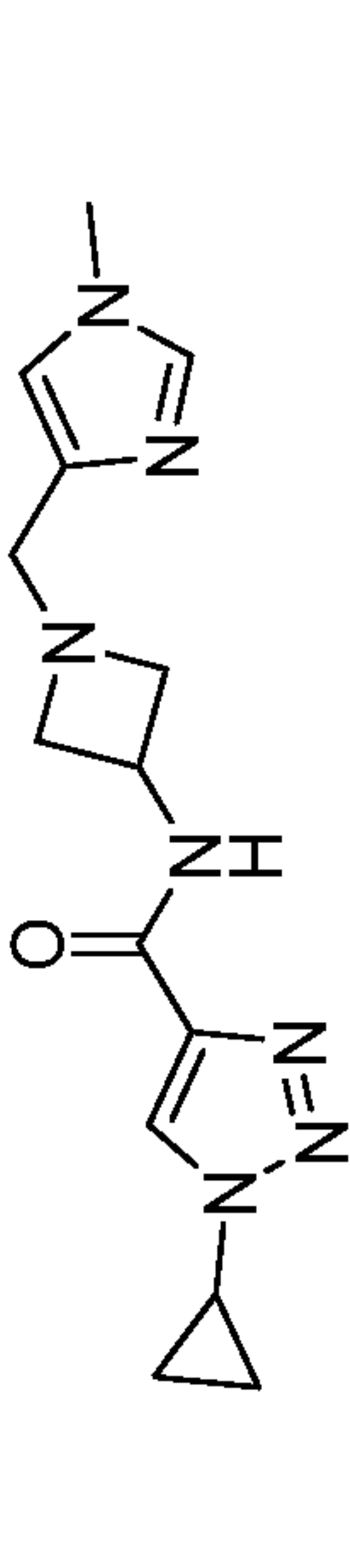
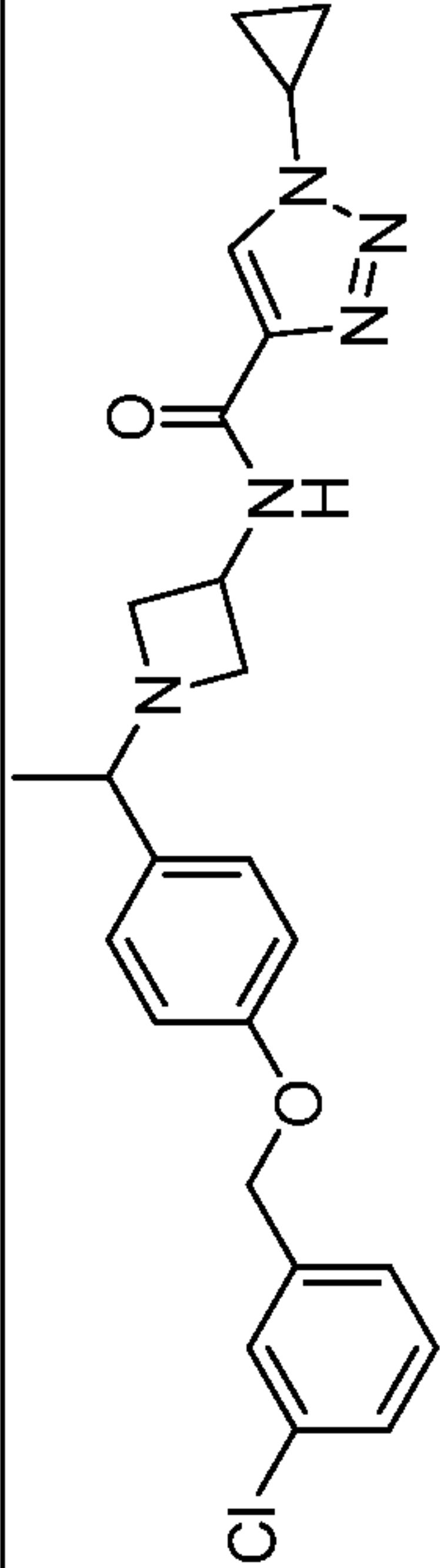
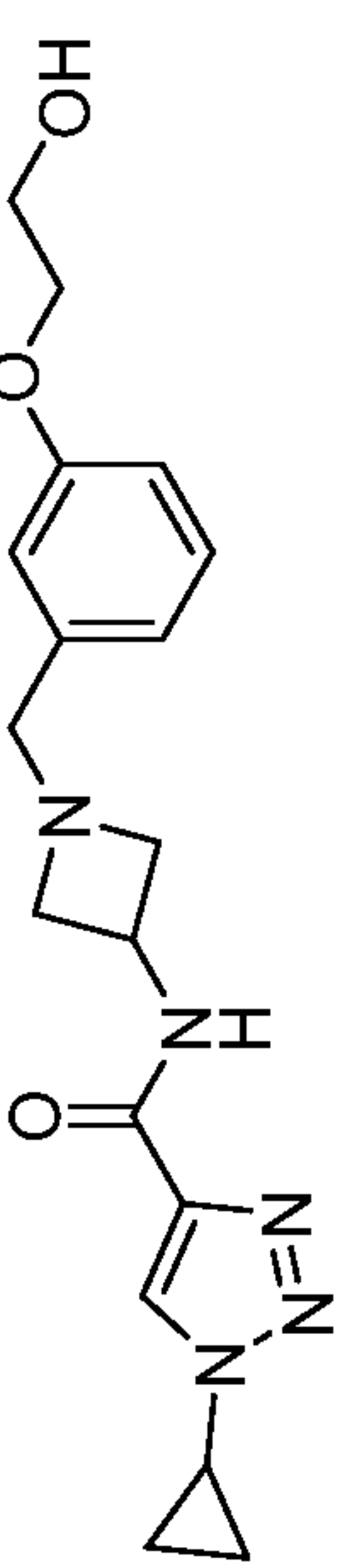
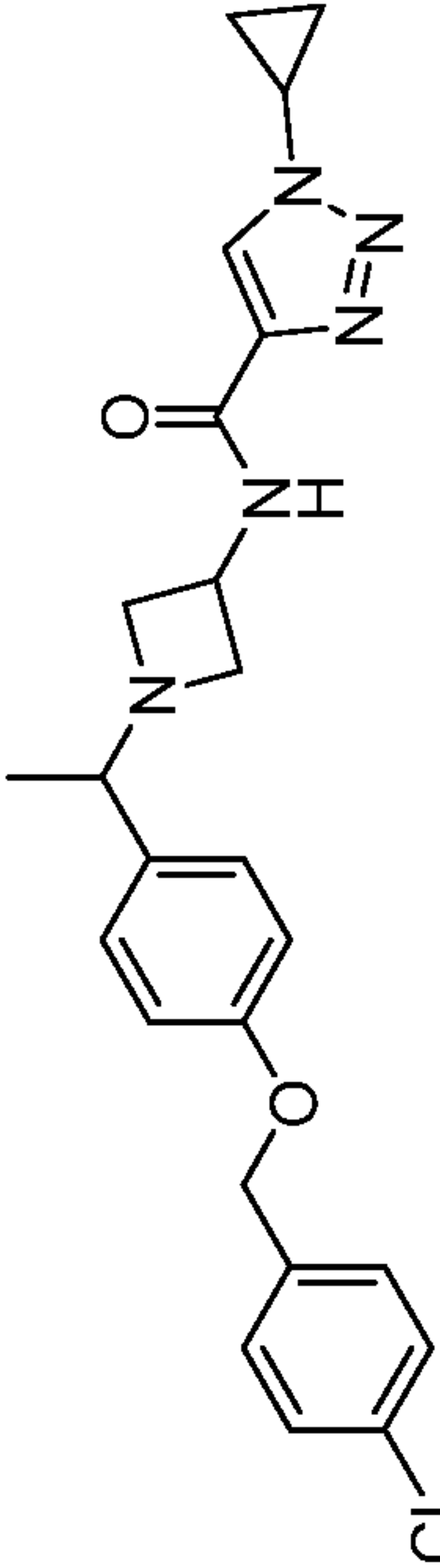
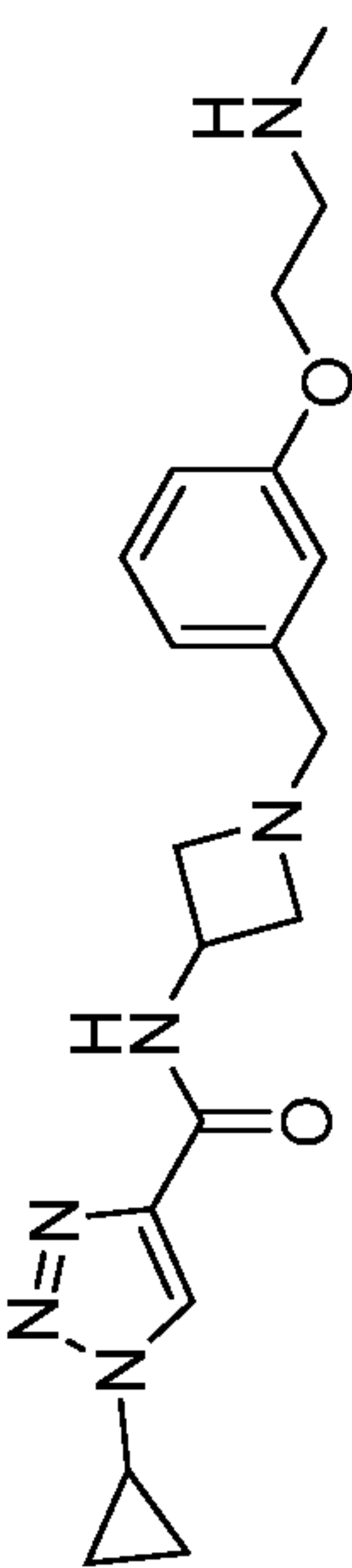
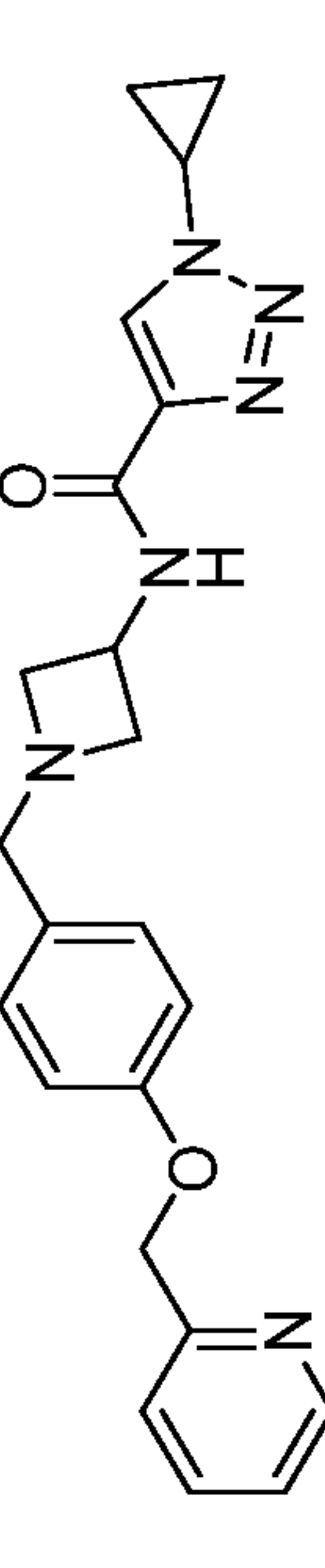
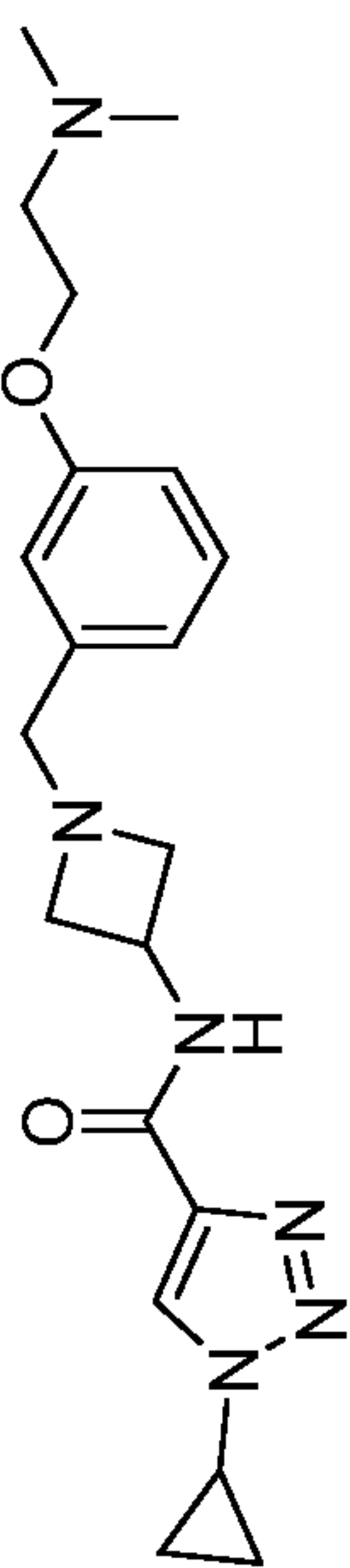
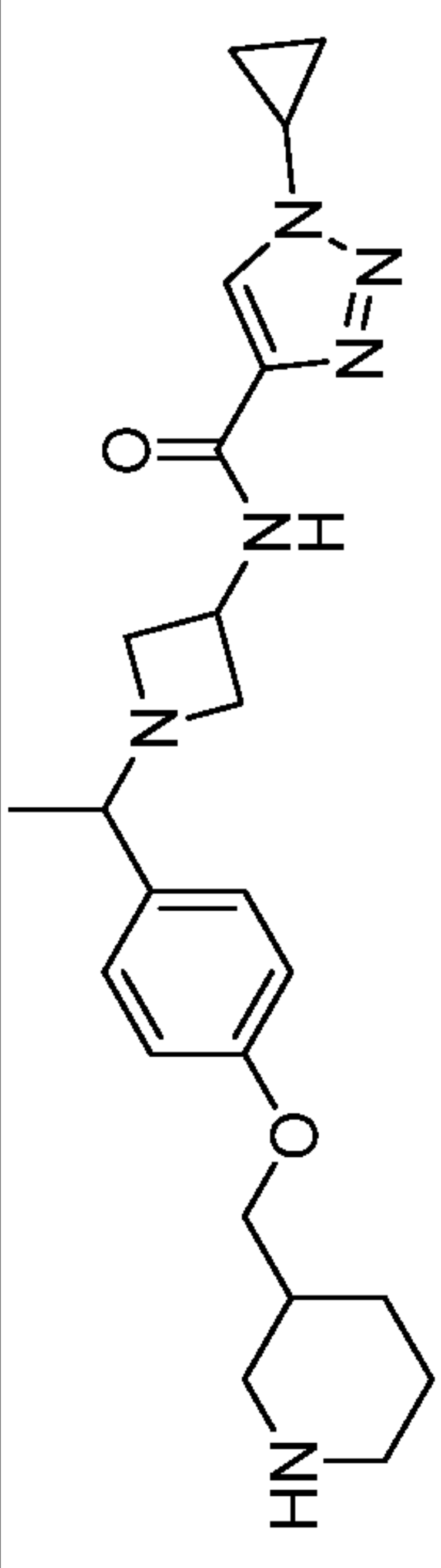
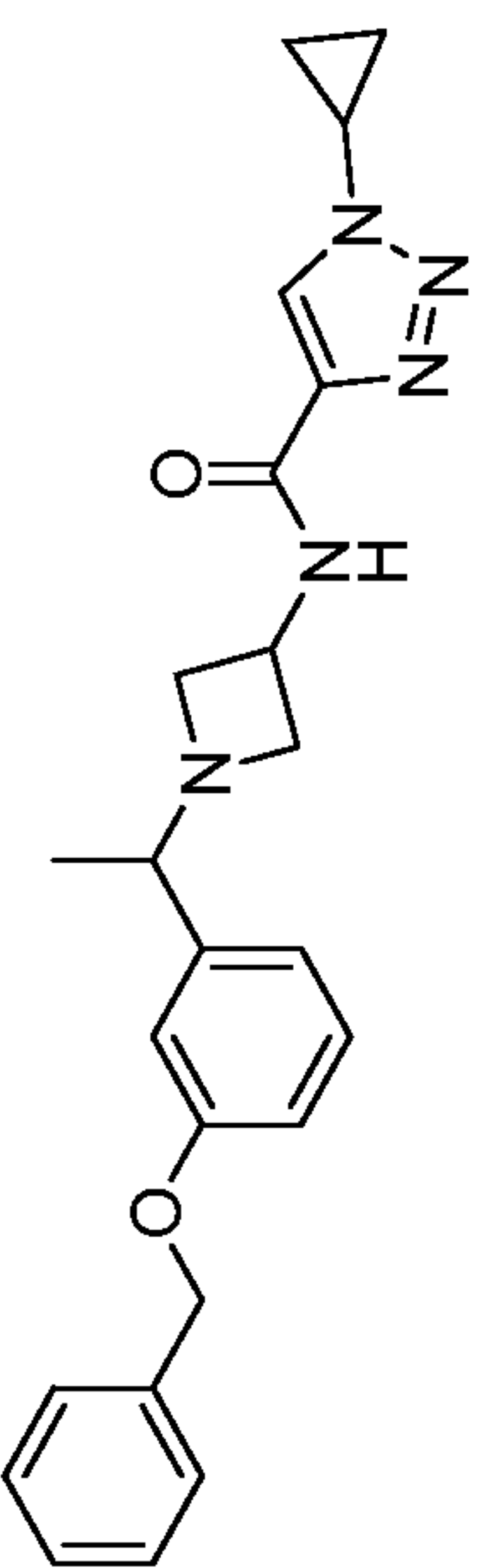
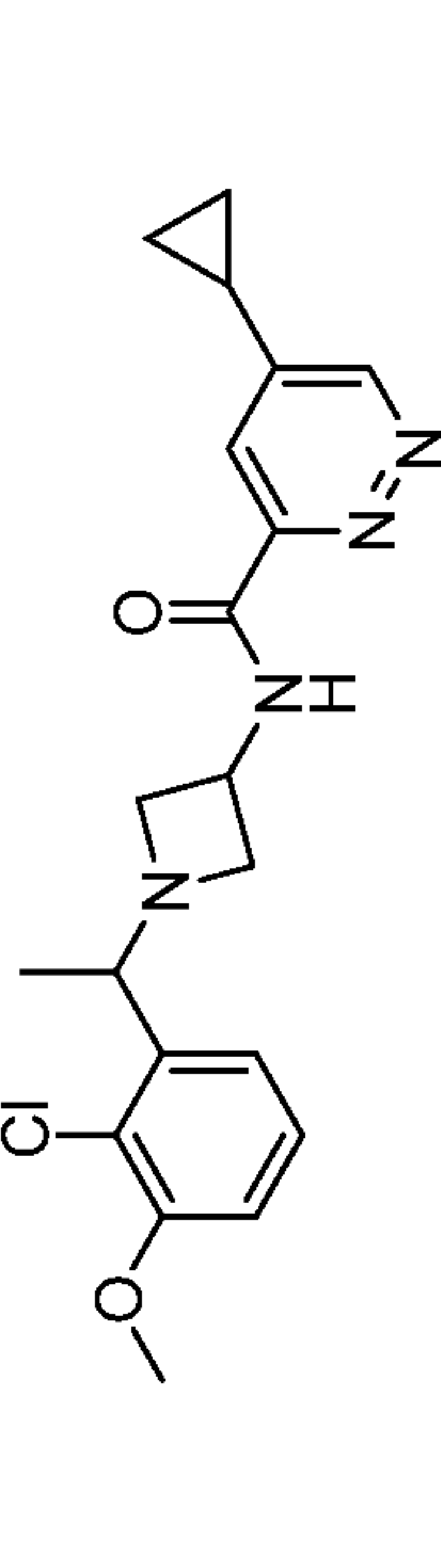
710		None	824		None
711		None	825		None
712		None	826		None
713		None	827		None

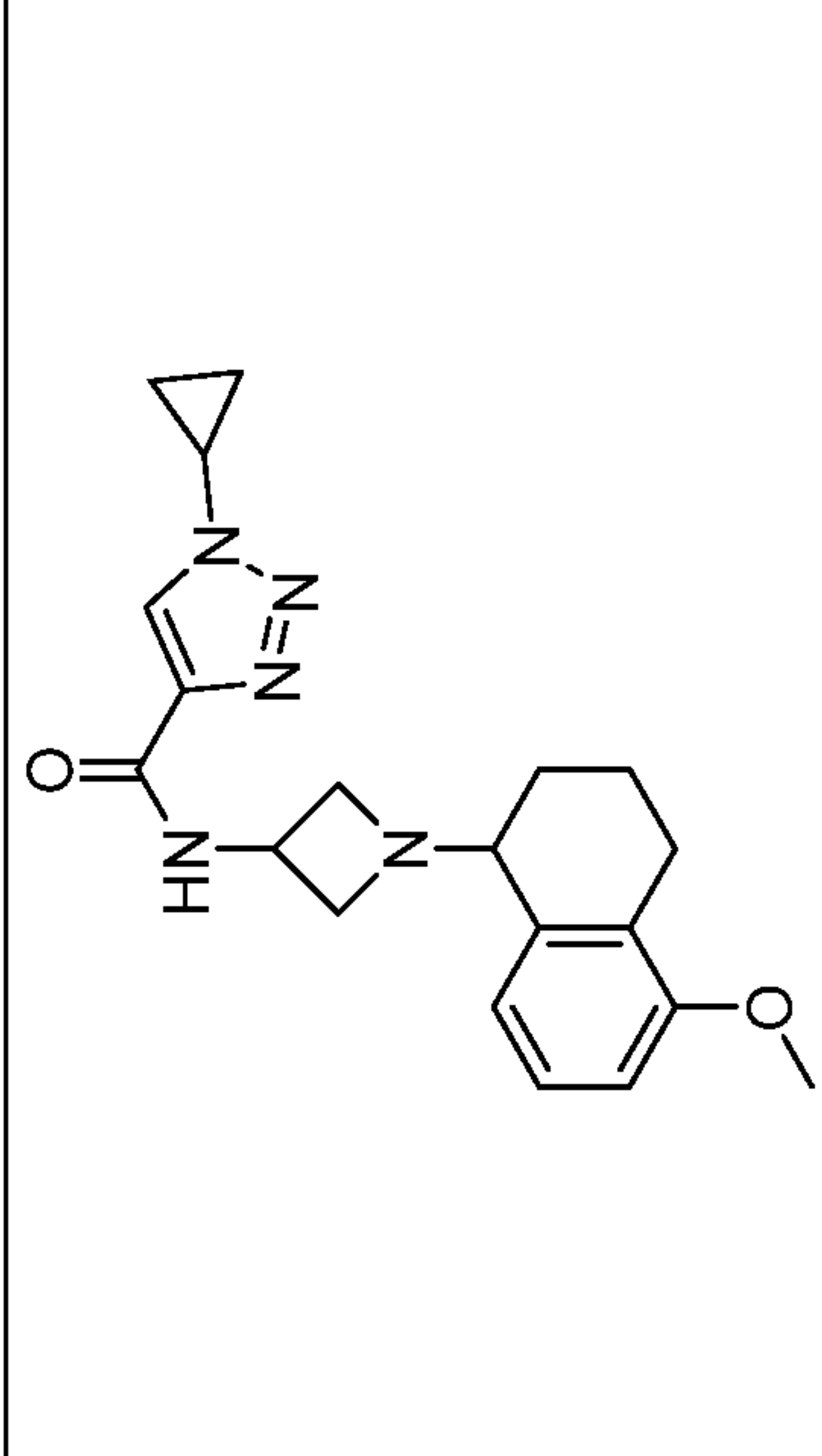
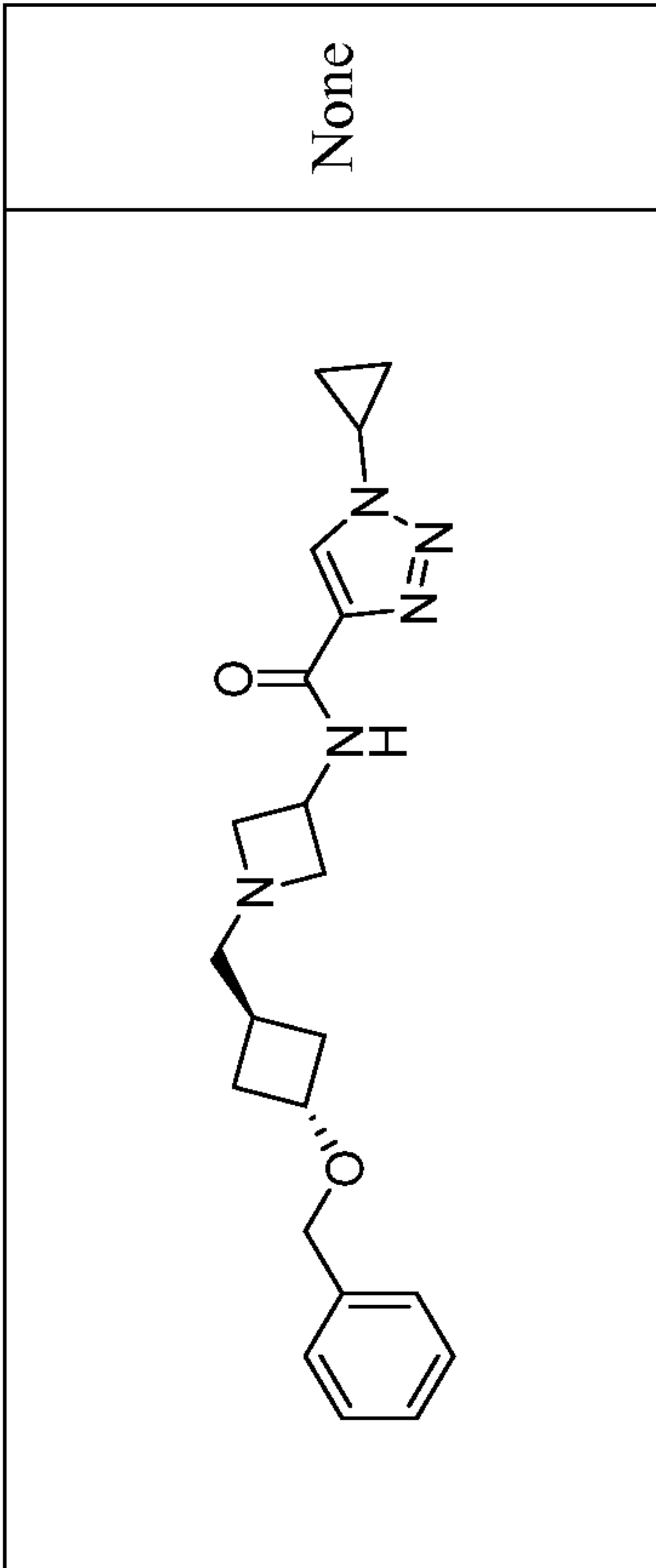
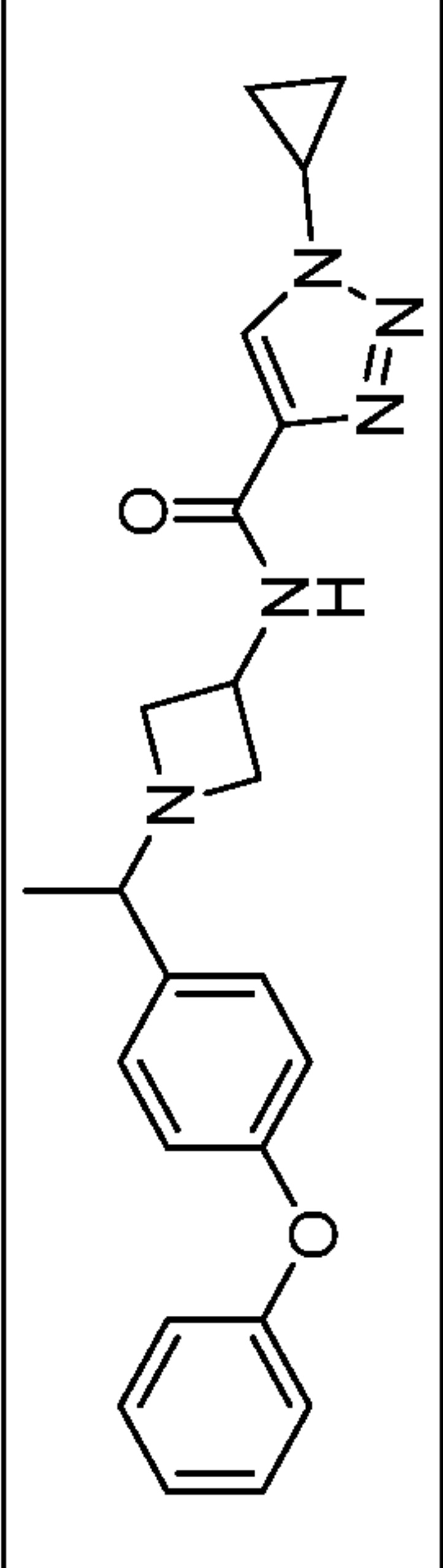
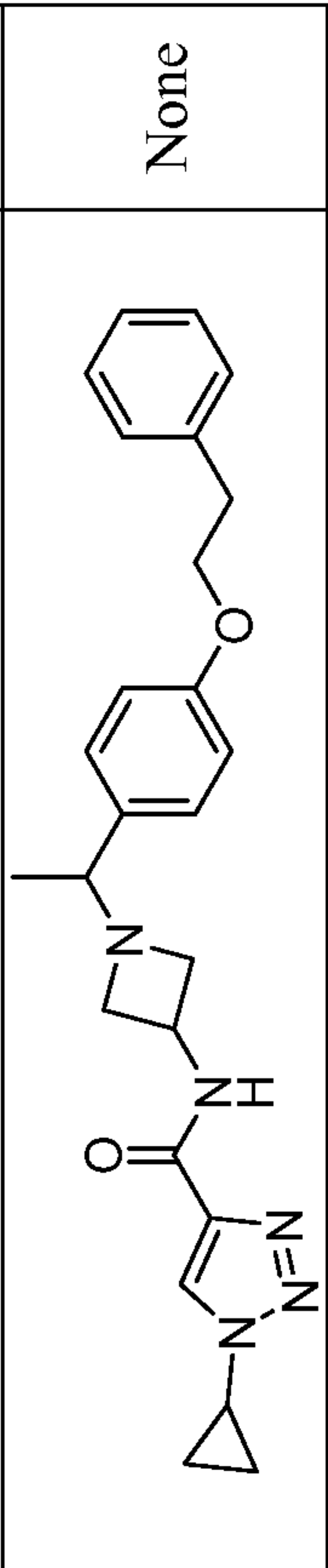
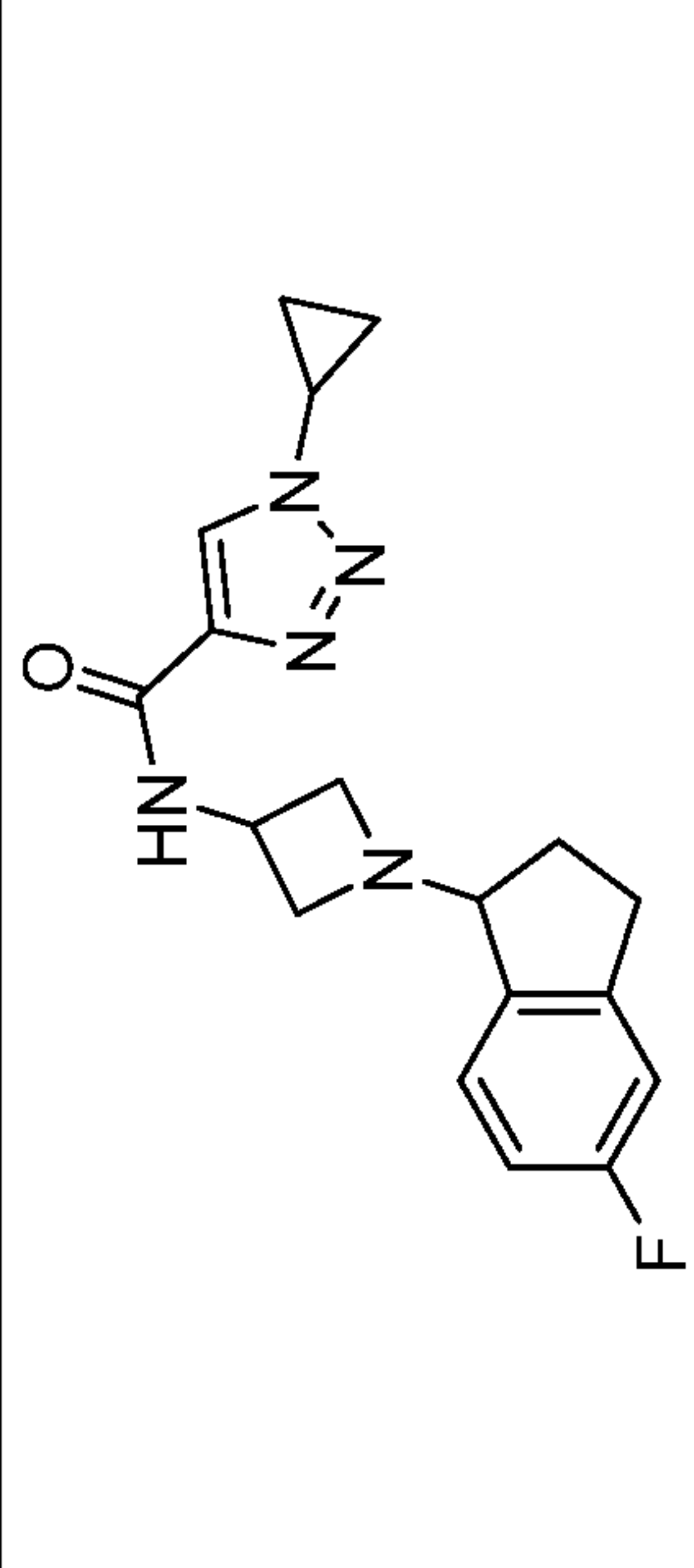
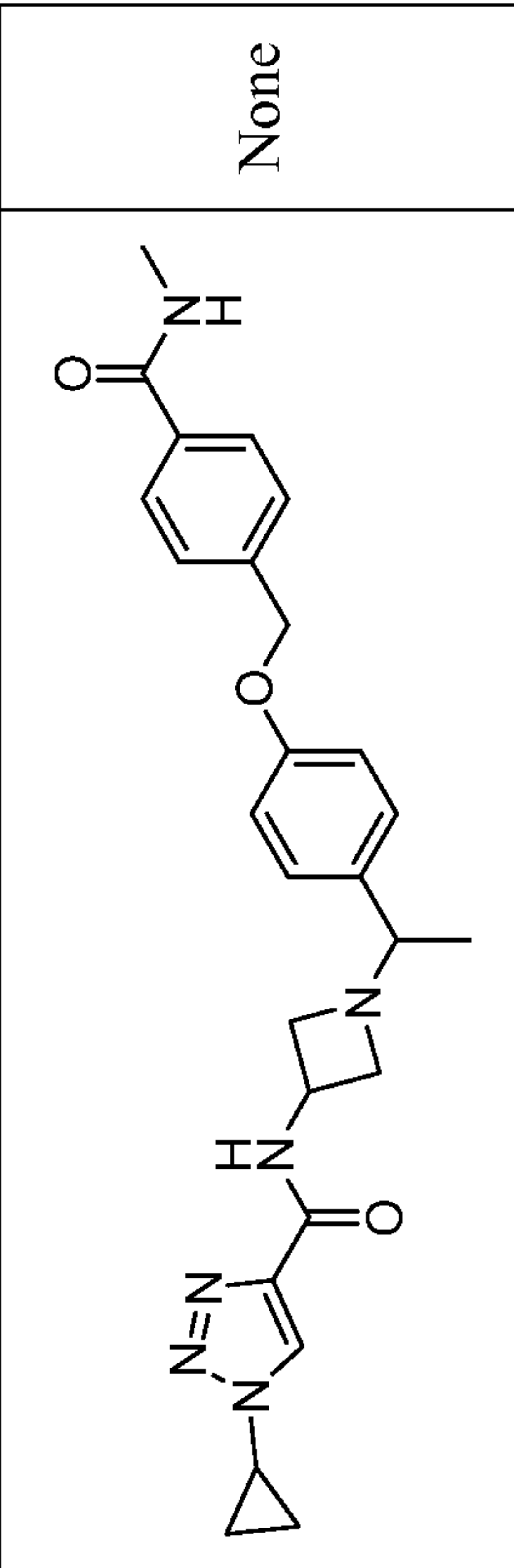
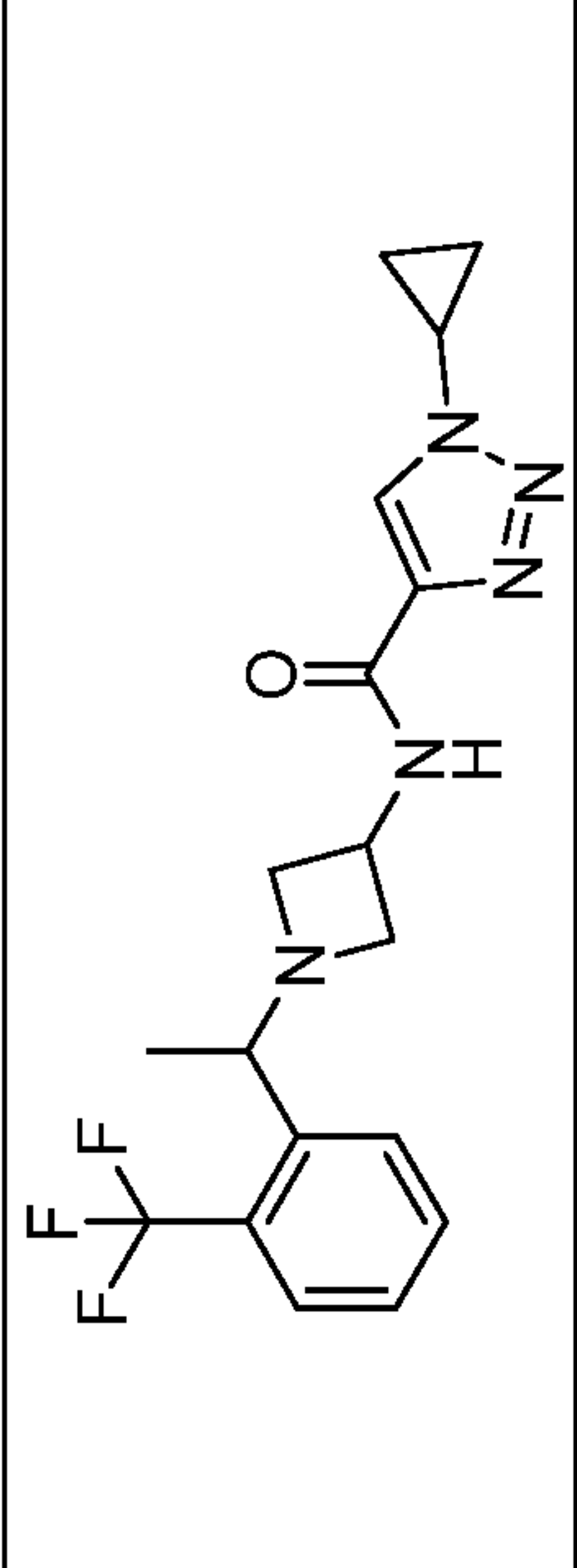
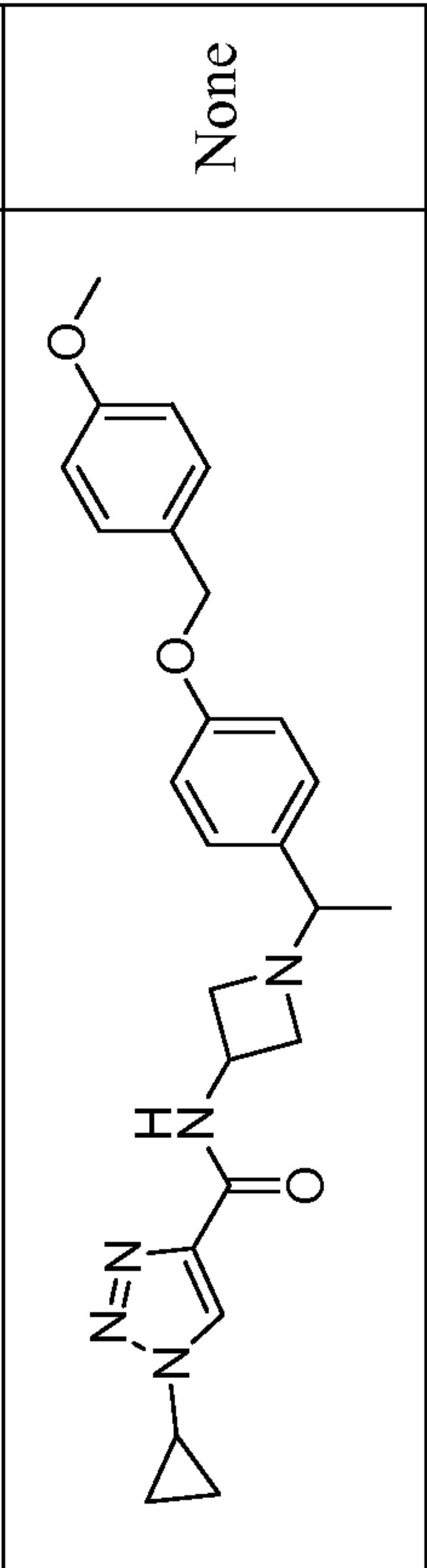
714		None	828		None
715		None	829		None
716		None	830		None
717		None	831		None
718		None	832		None

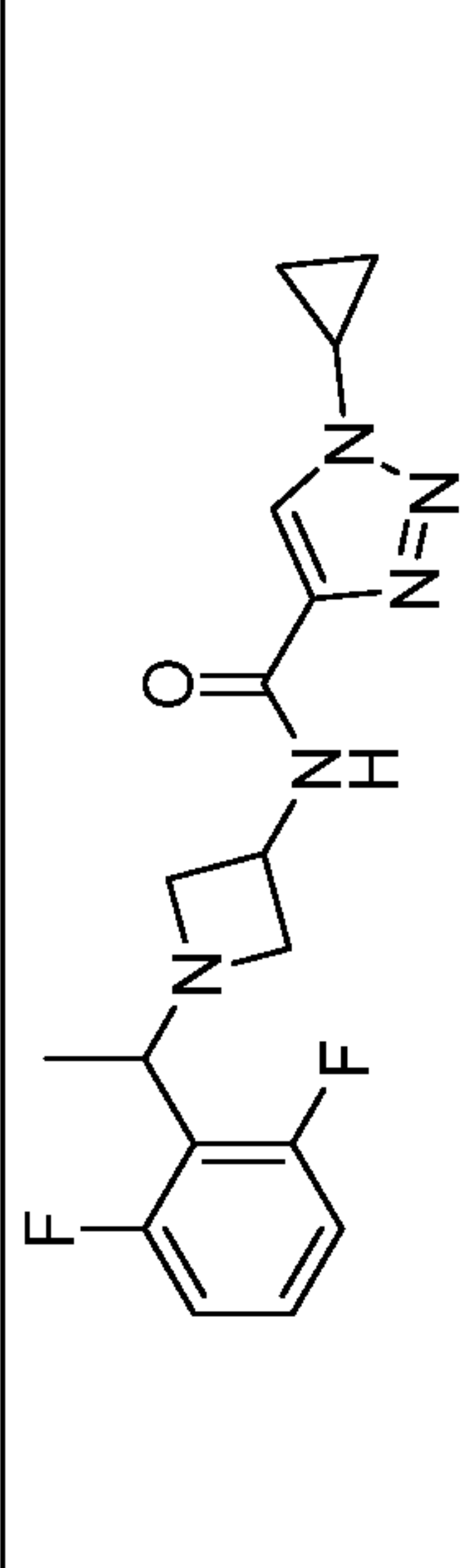
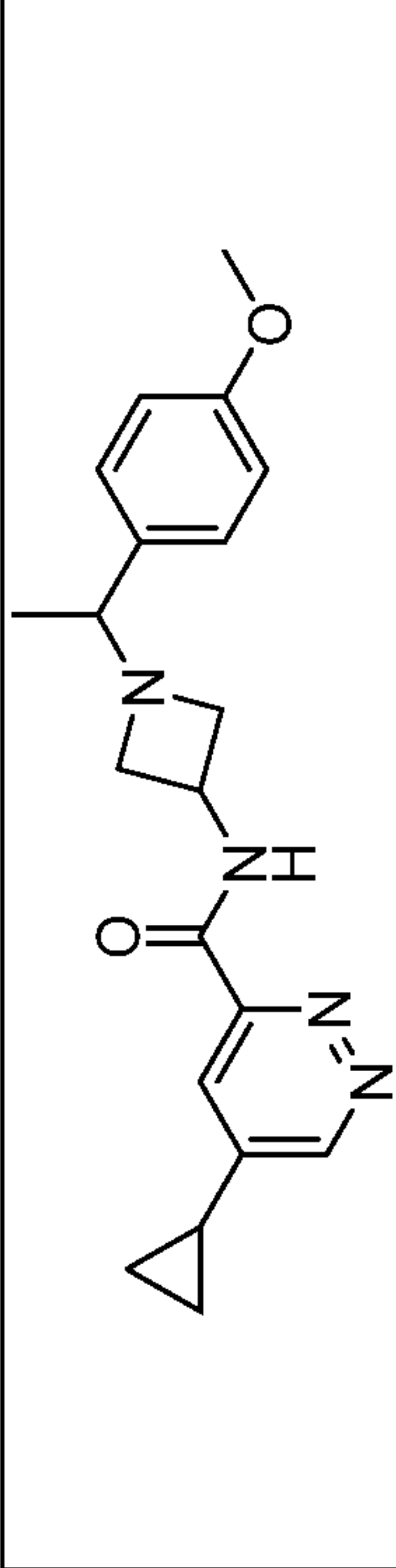
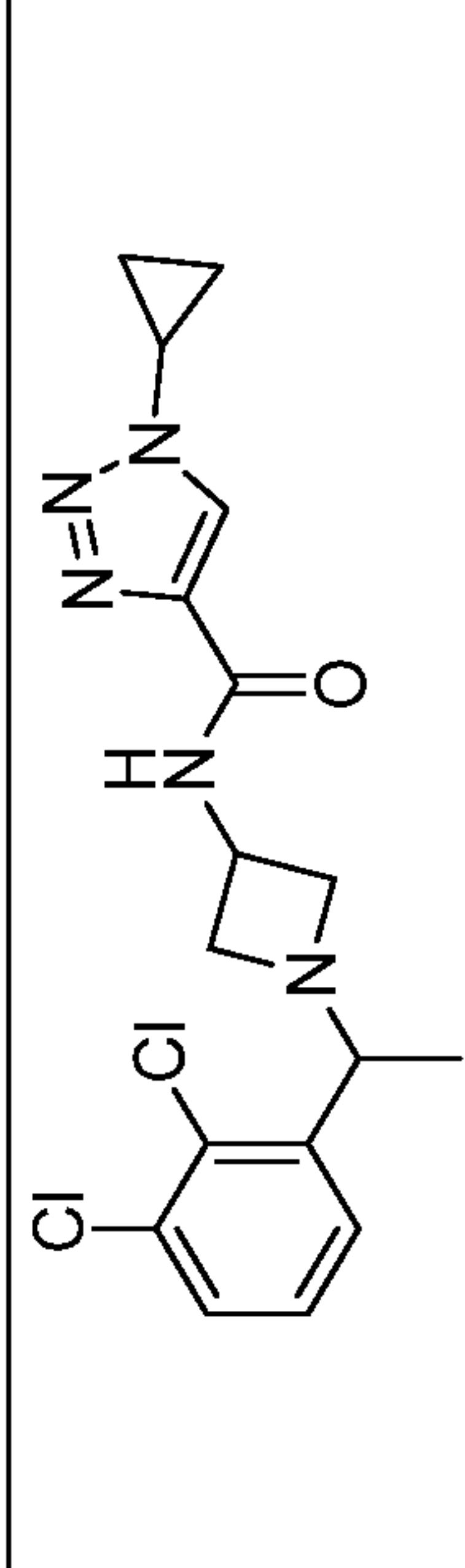
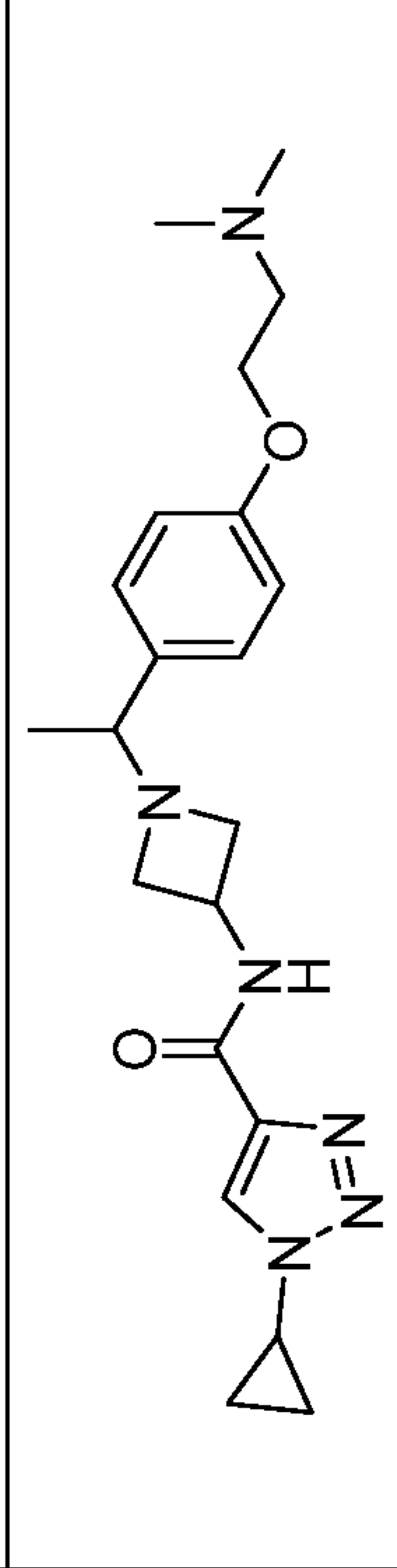
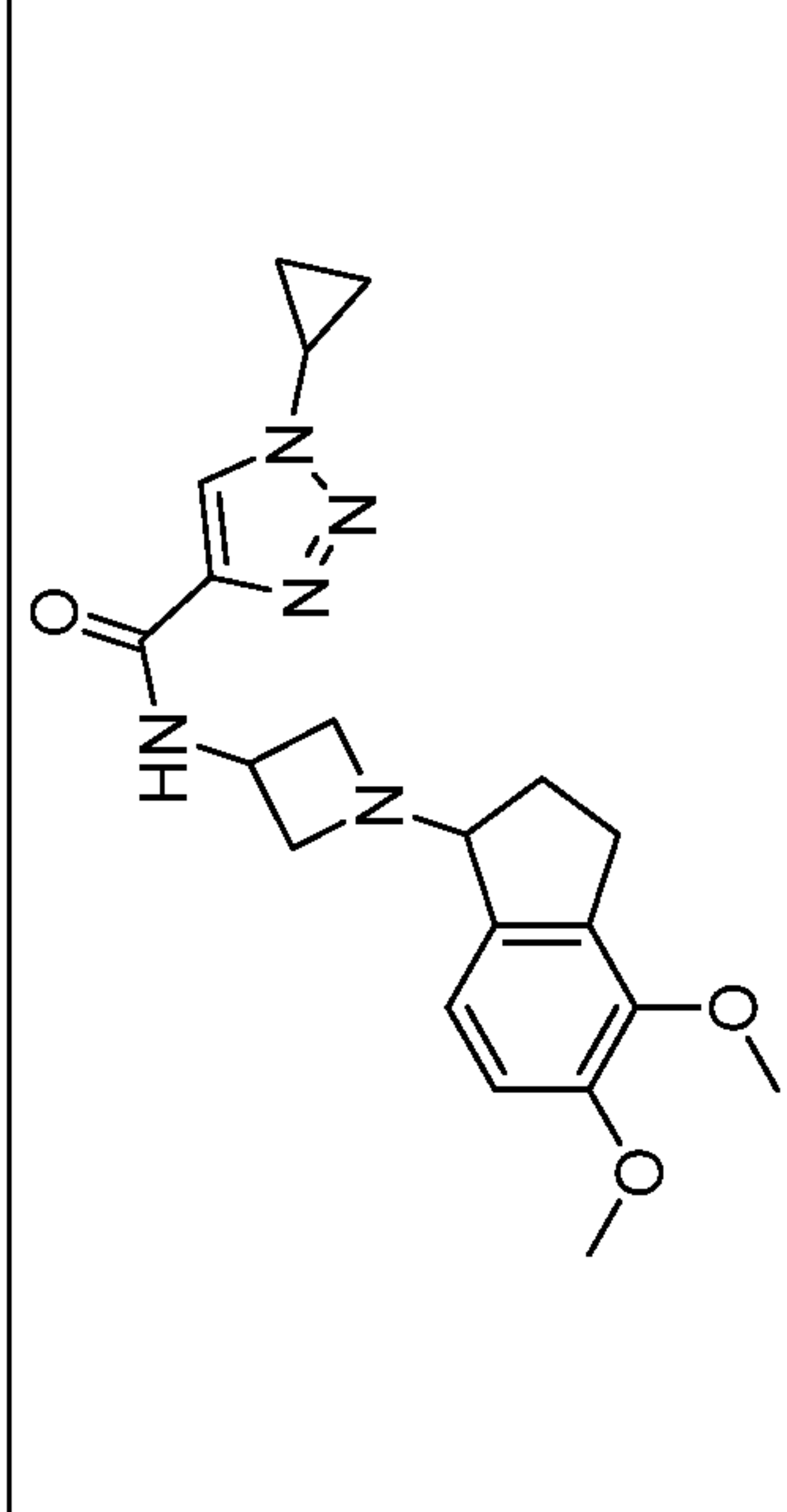
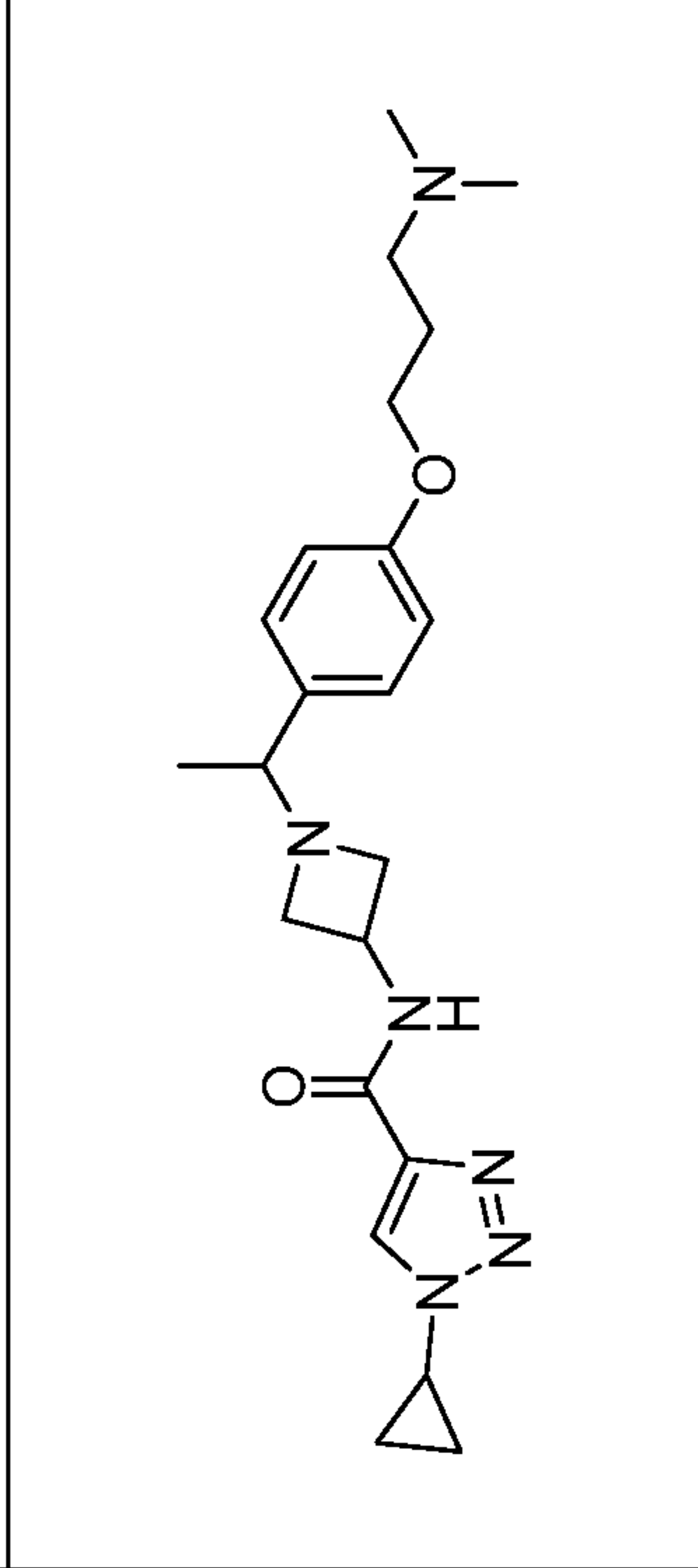
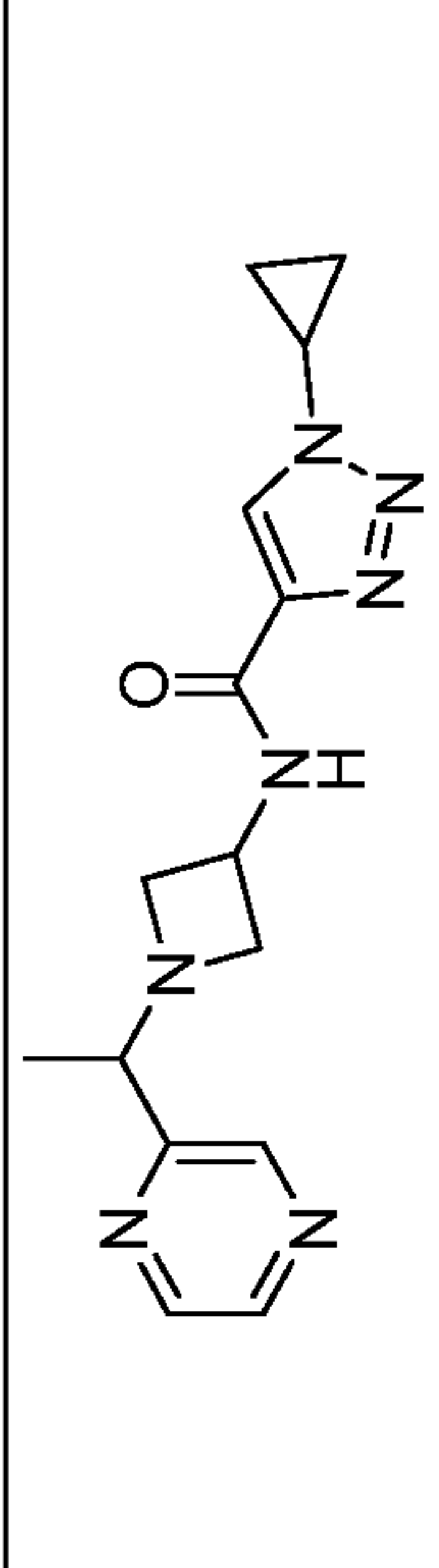
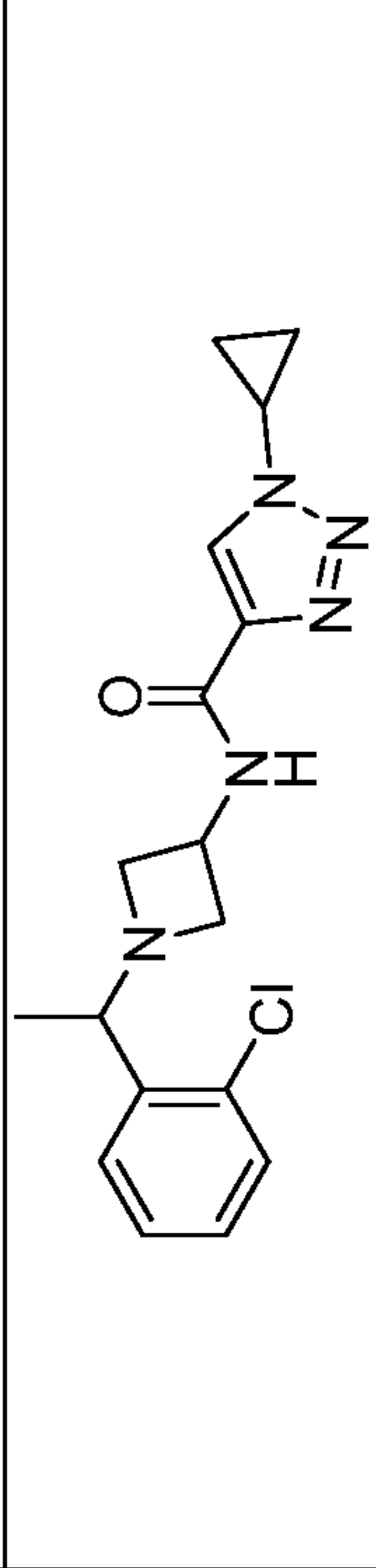
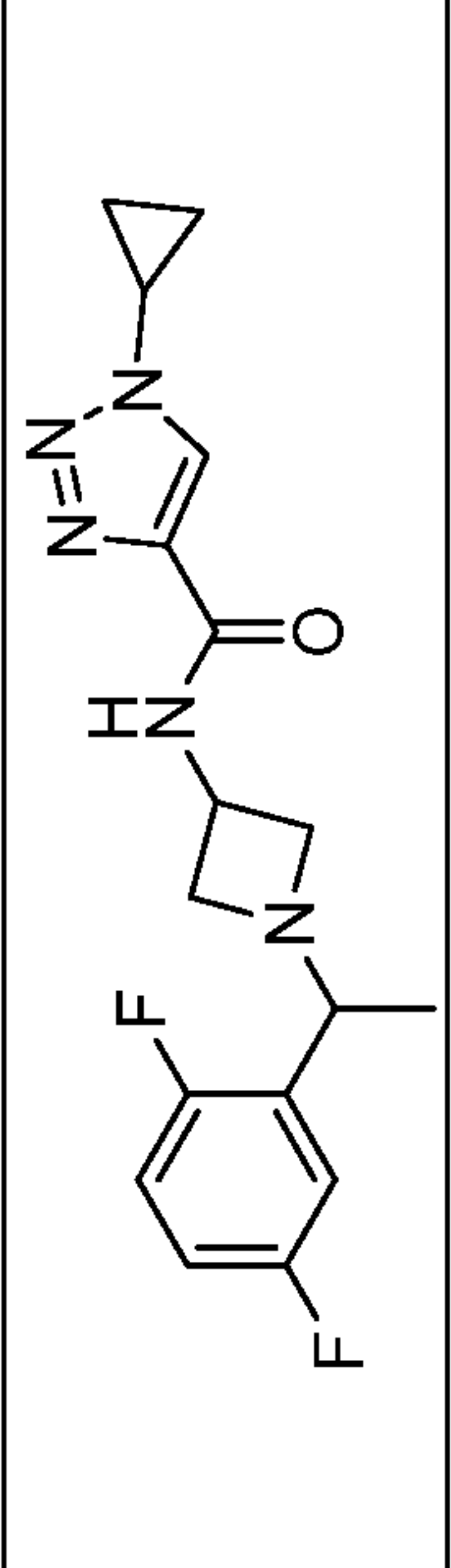
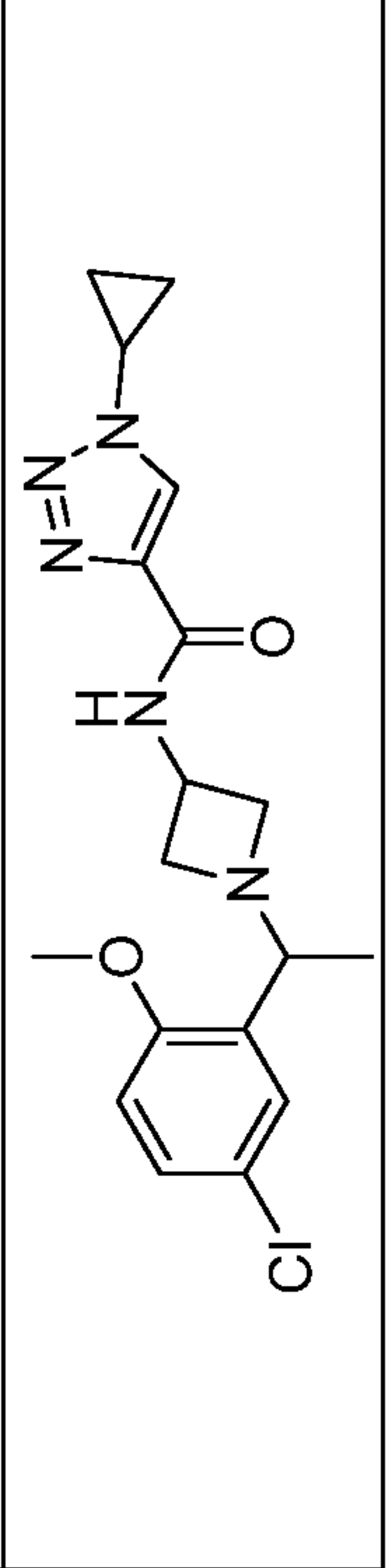
719		None	833		None
720		None	834		None
721		None	835		None
722		None	836		None

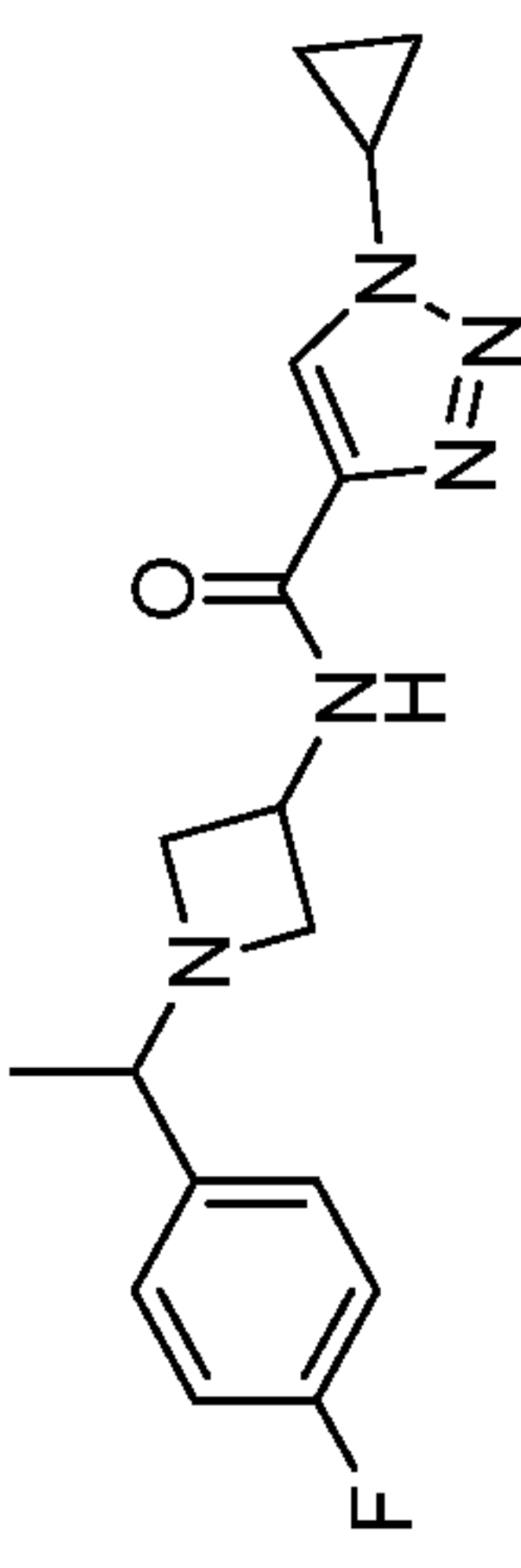
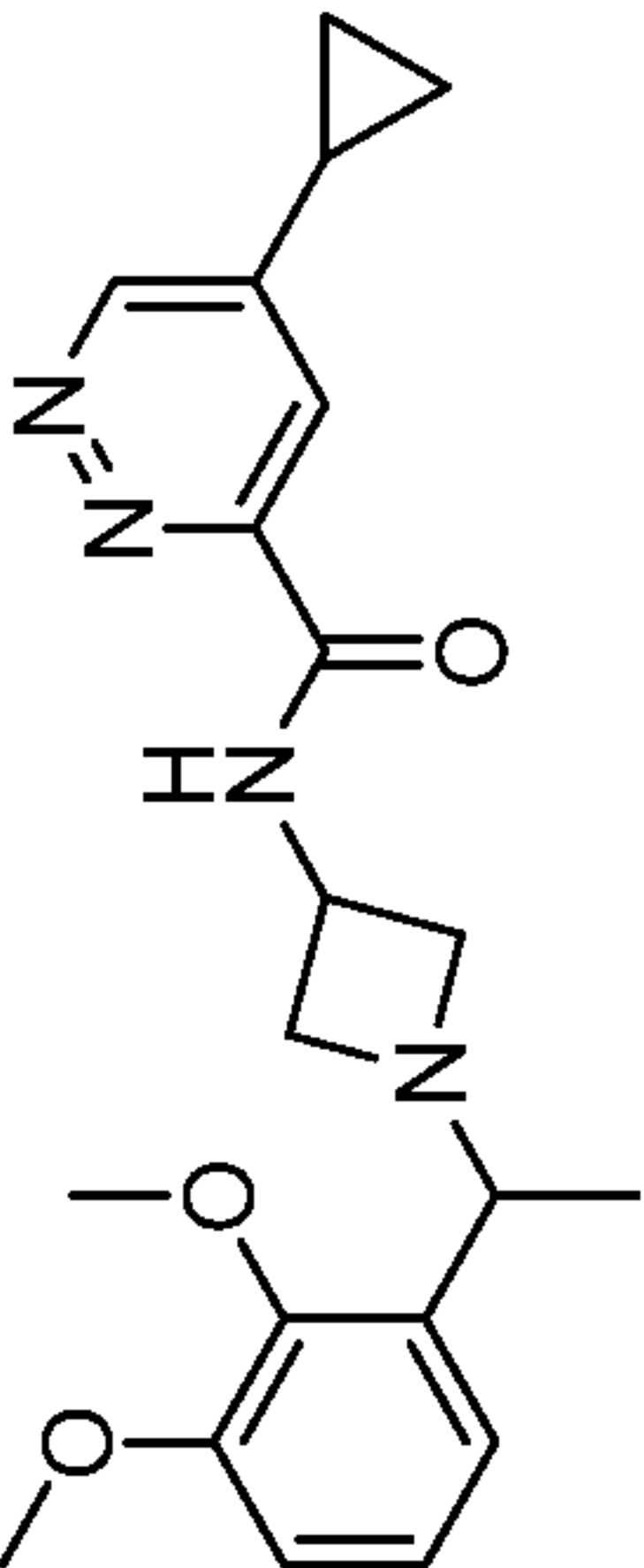
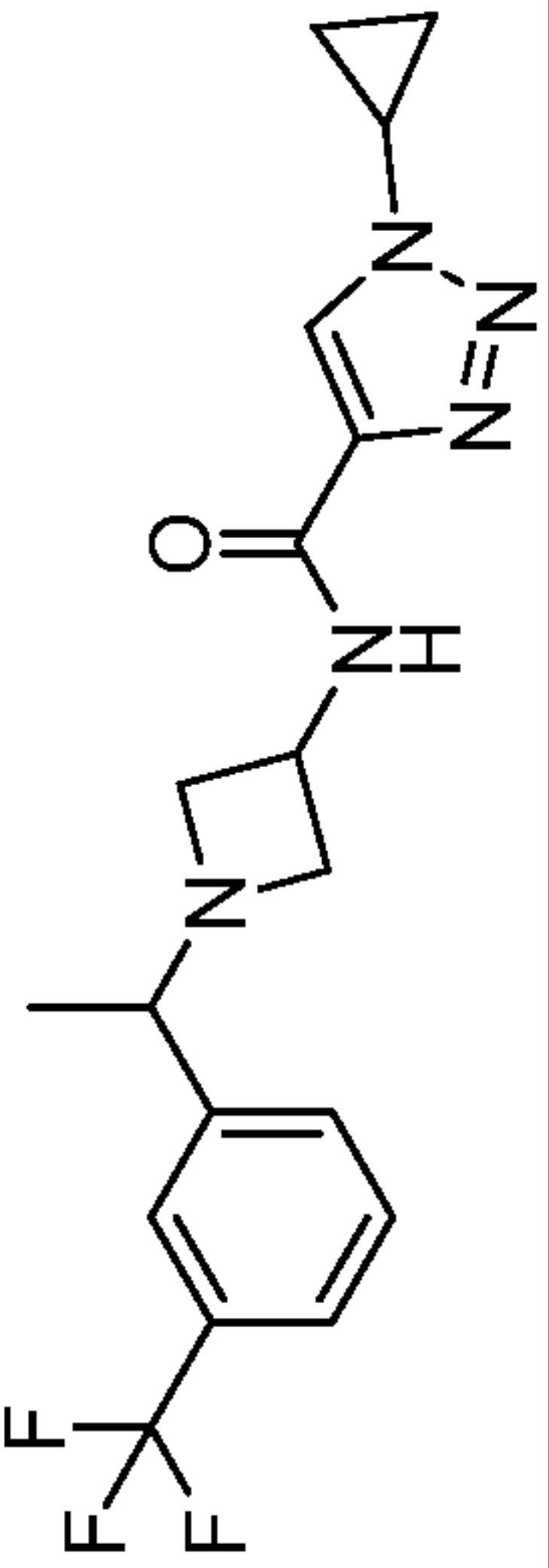
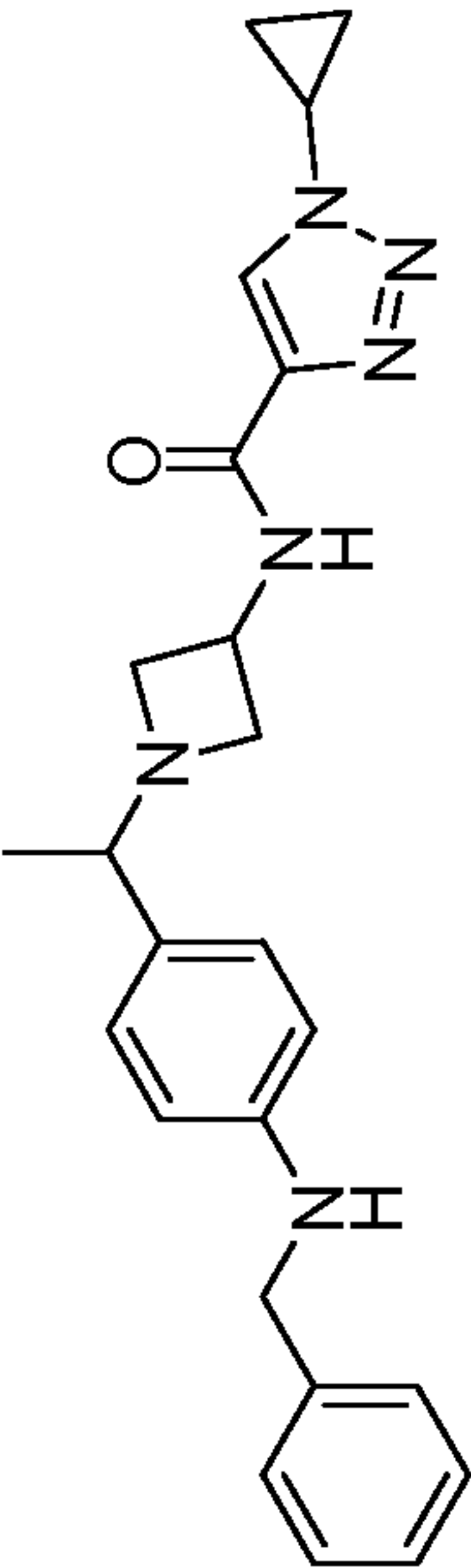
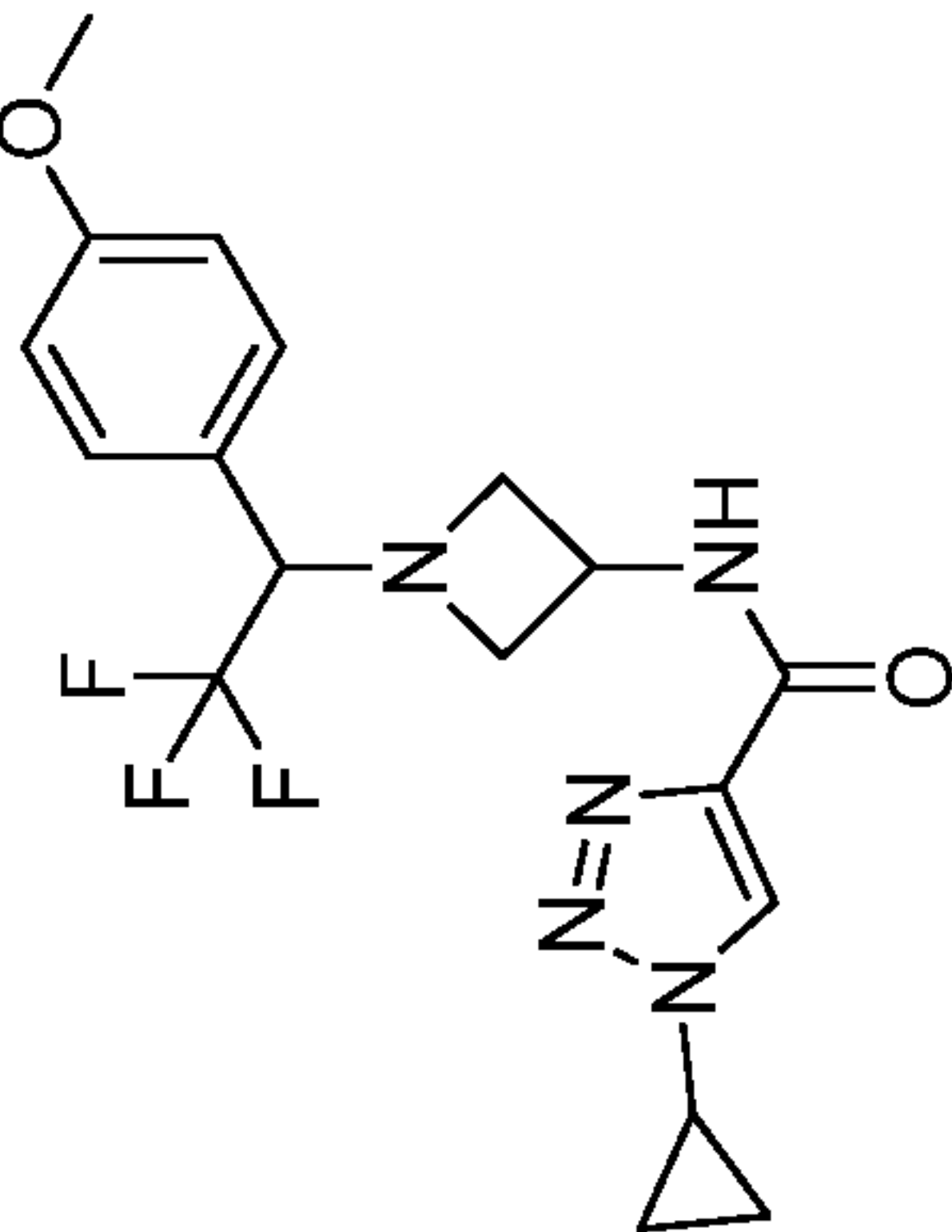
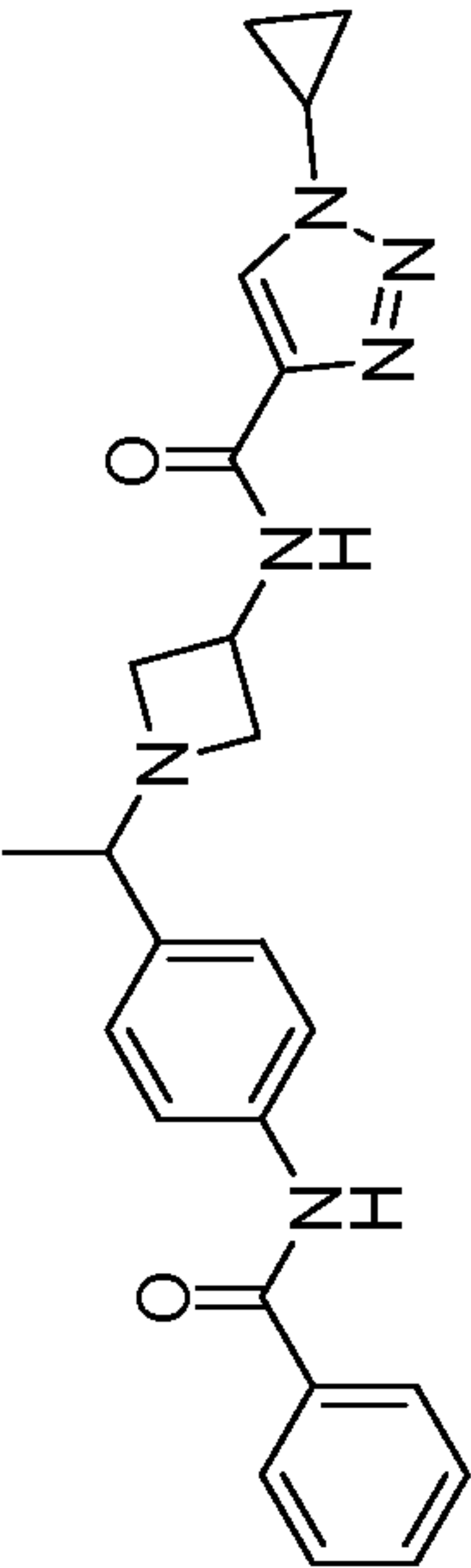
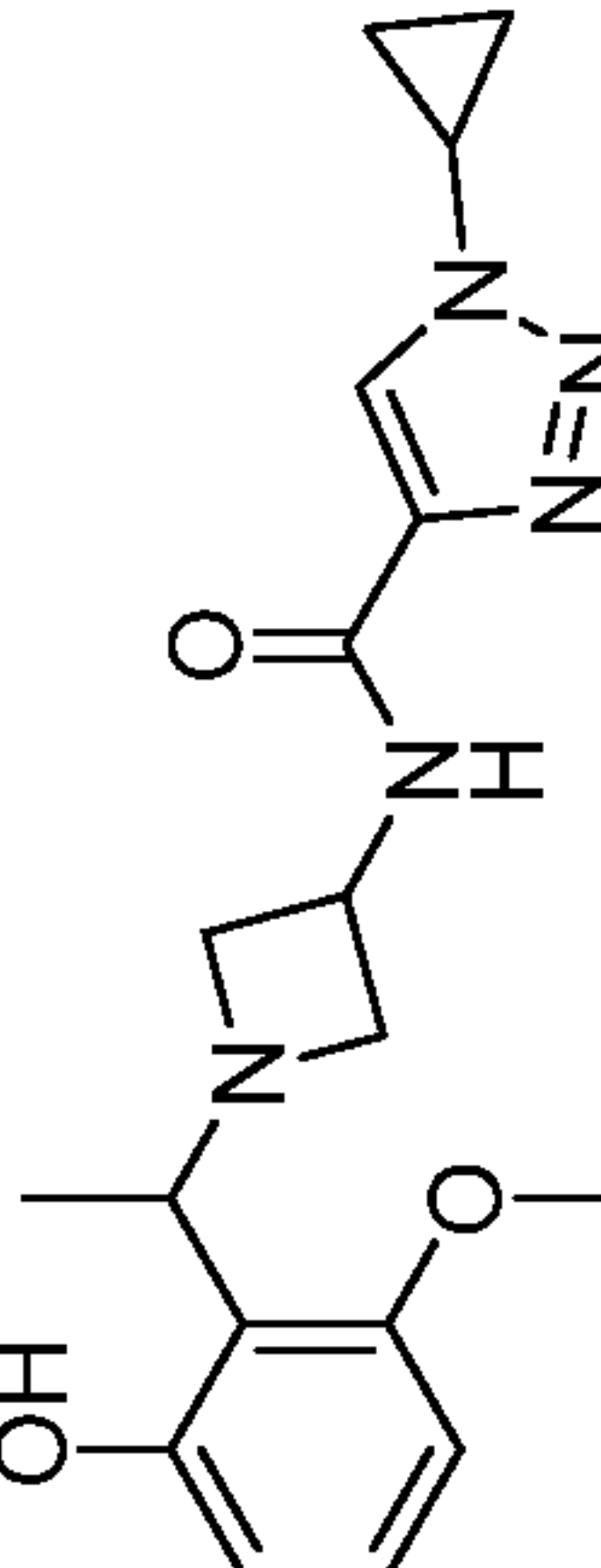
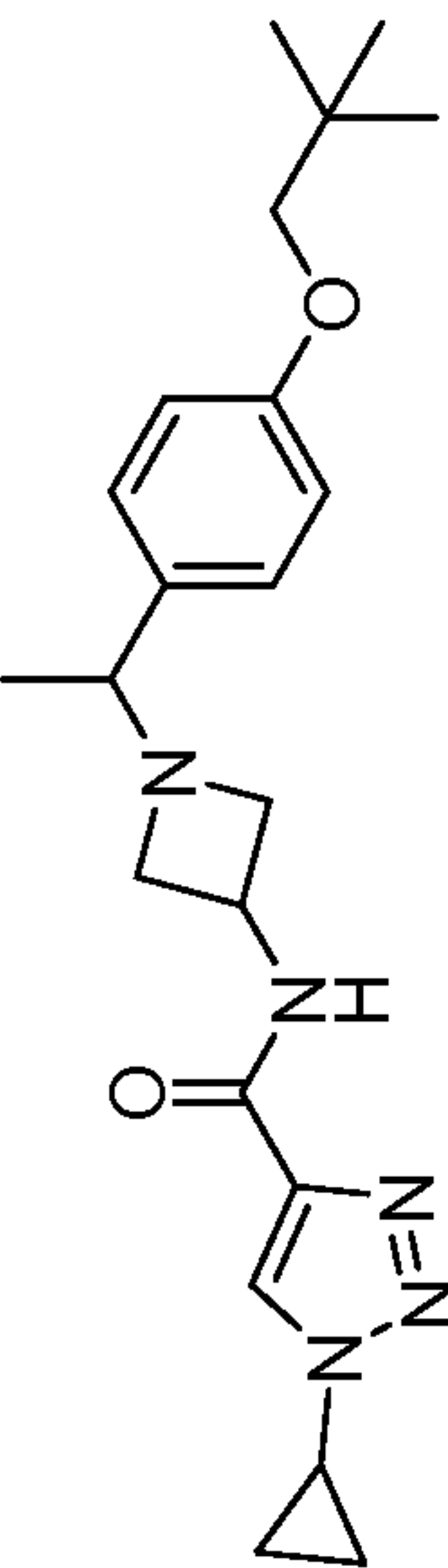
723		None	837		None
724		None	838		None
725		None	839		None
726		None	840		None
727		None	841		None

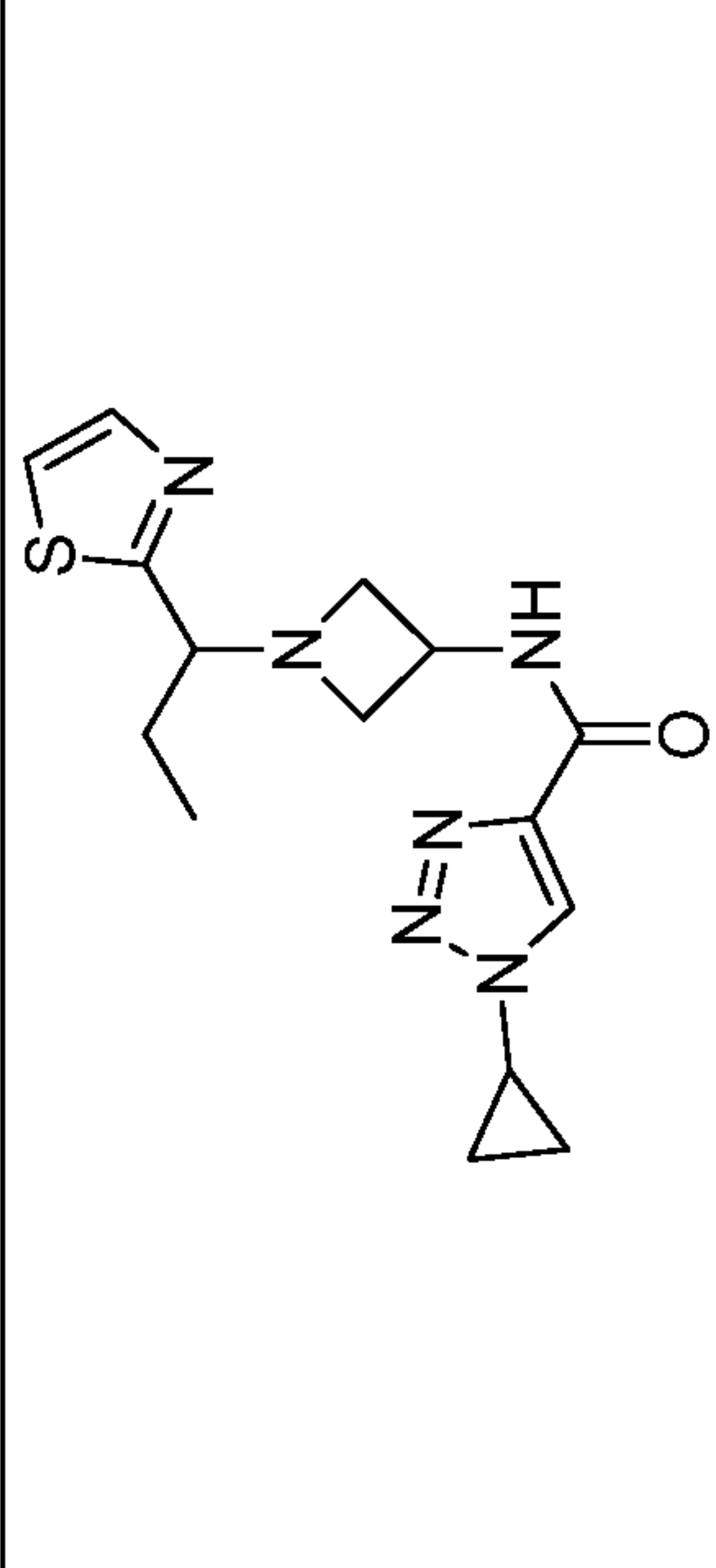
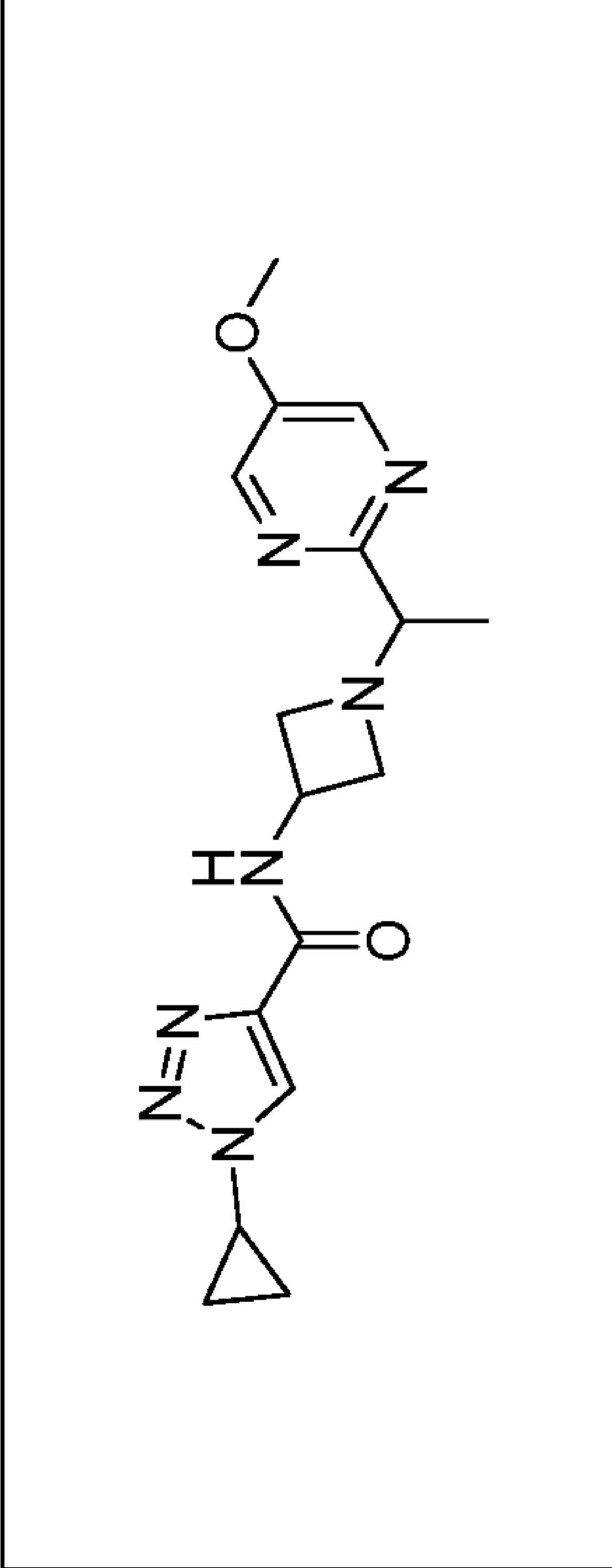
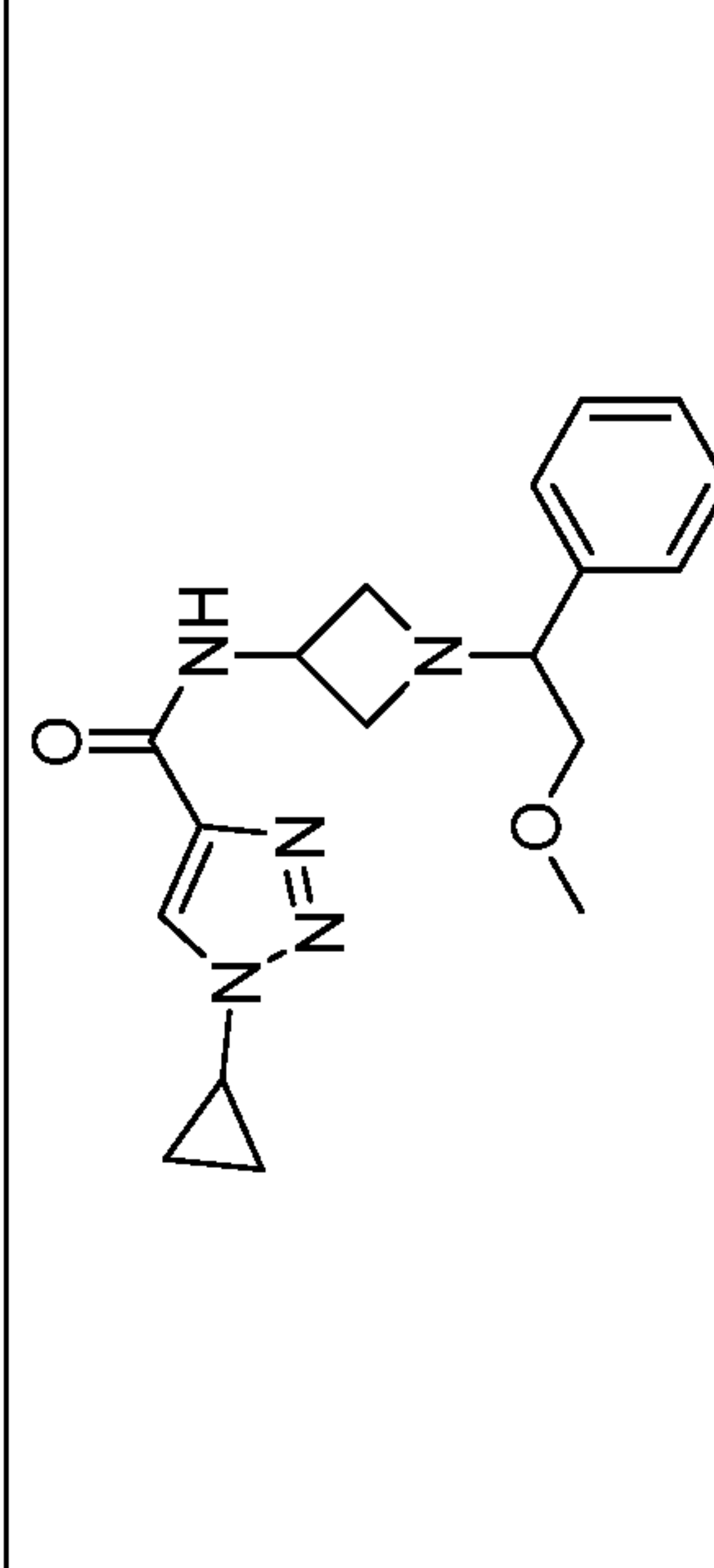
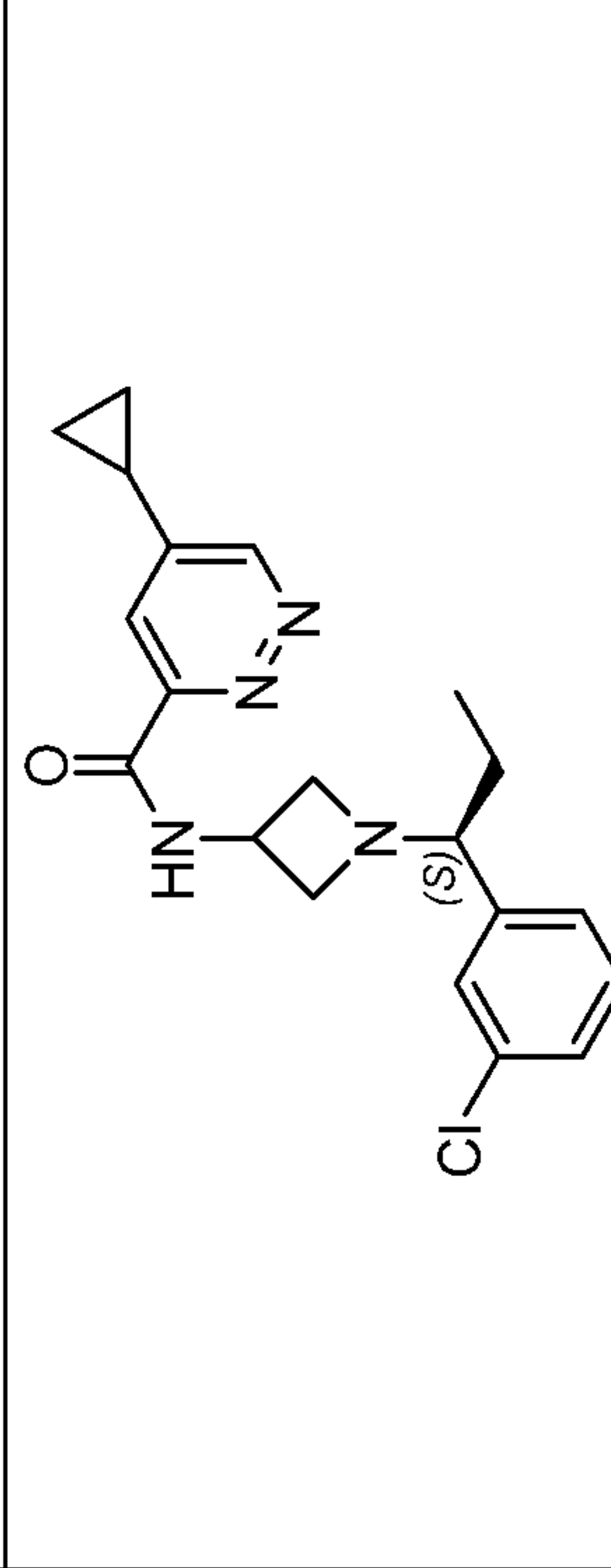
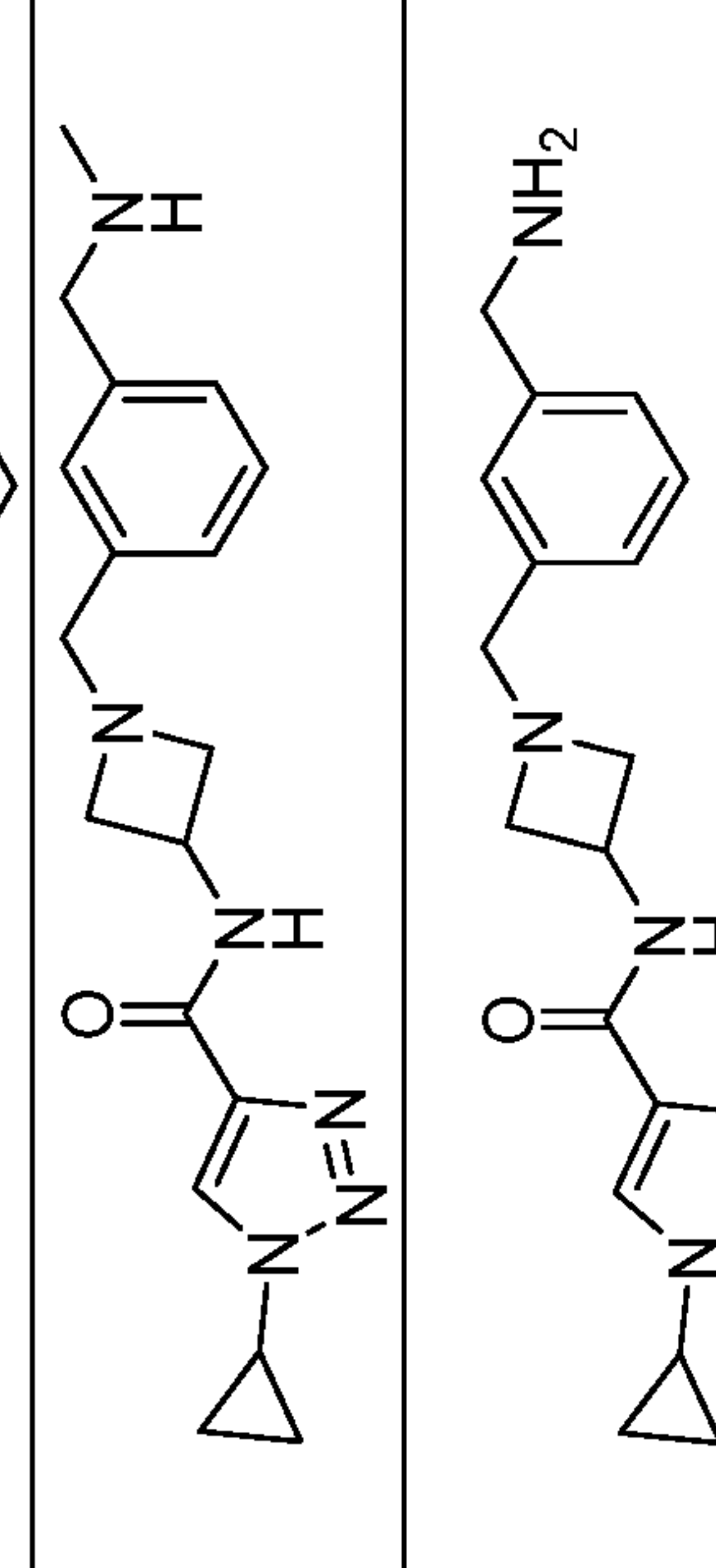
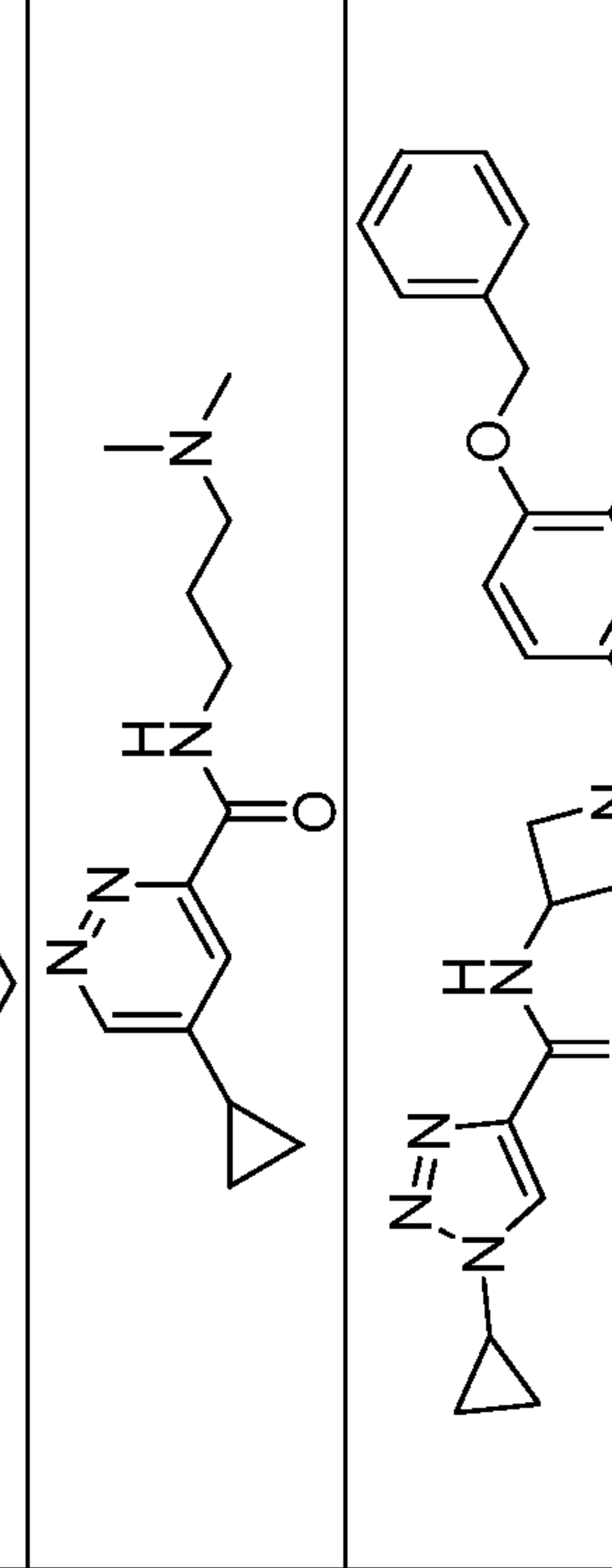
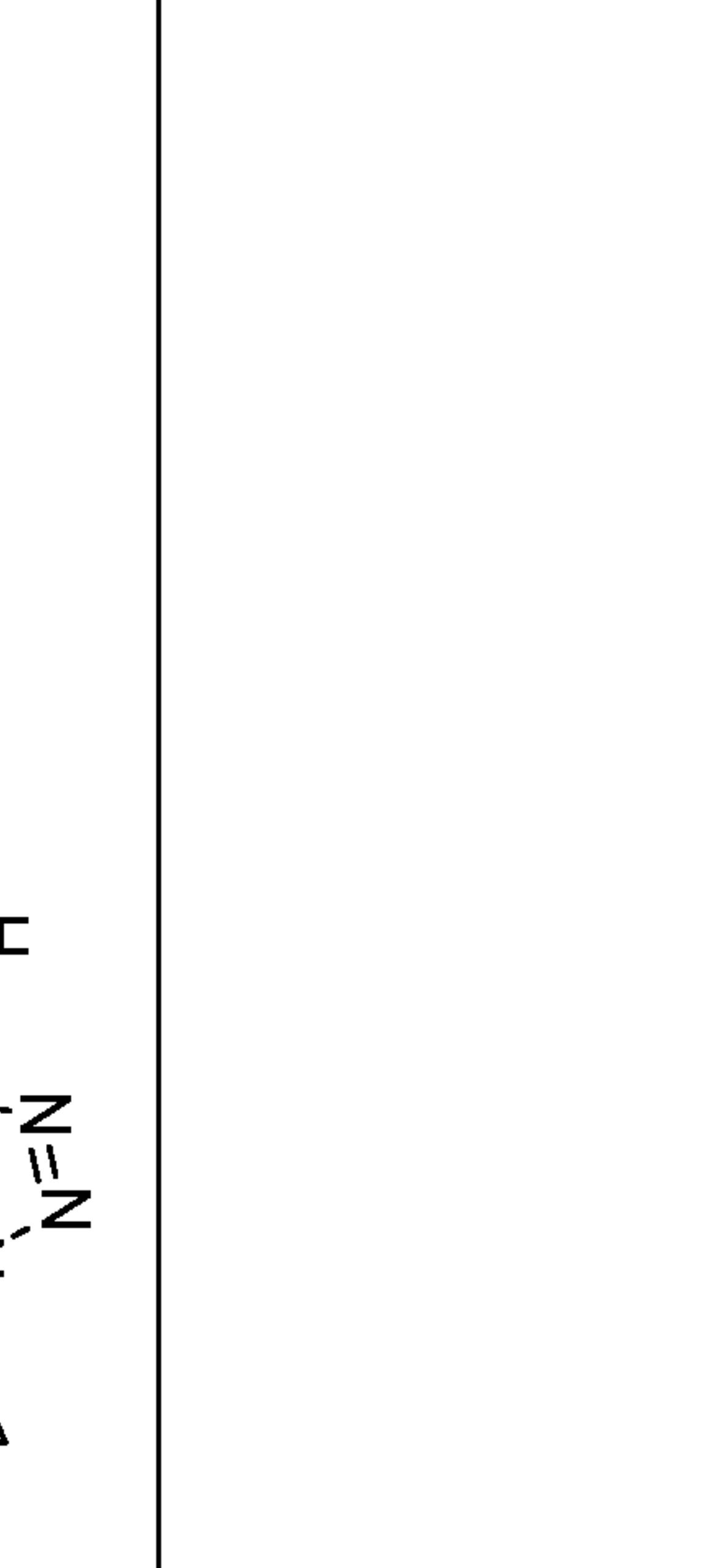
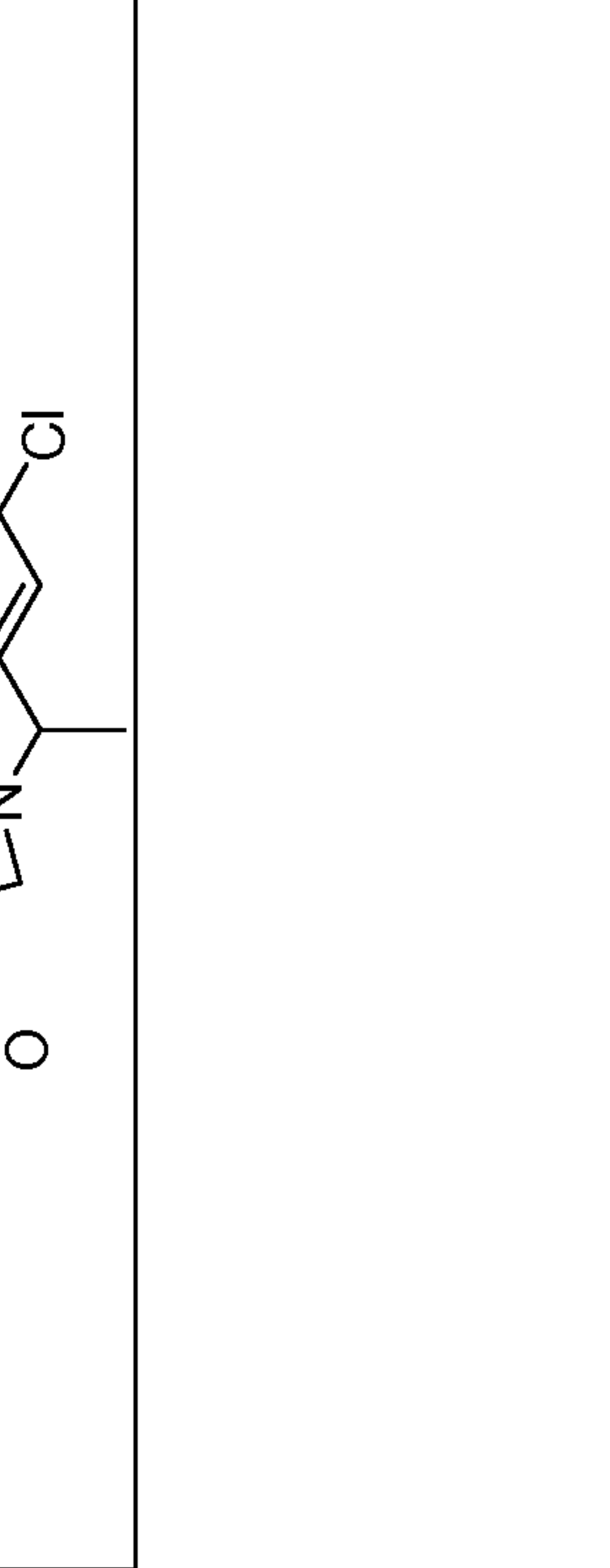
728		None	842		None
729		None	843		None
730		None	844		None
731		None	845		None
732		None	846		None

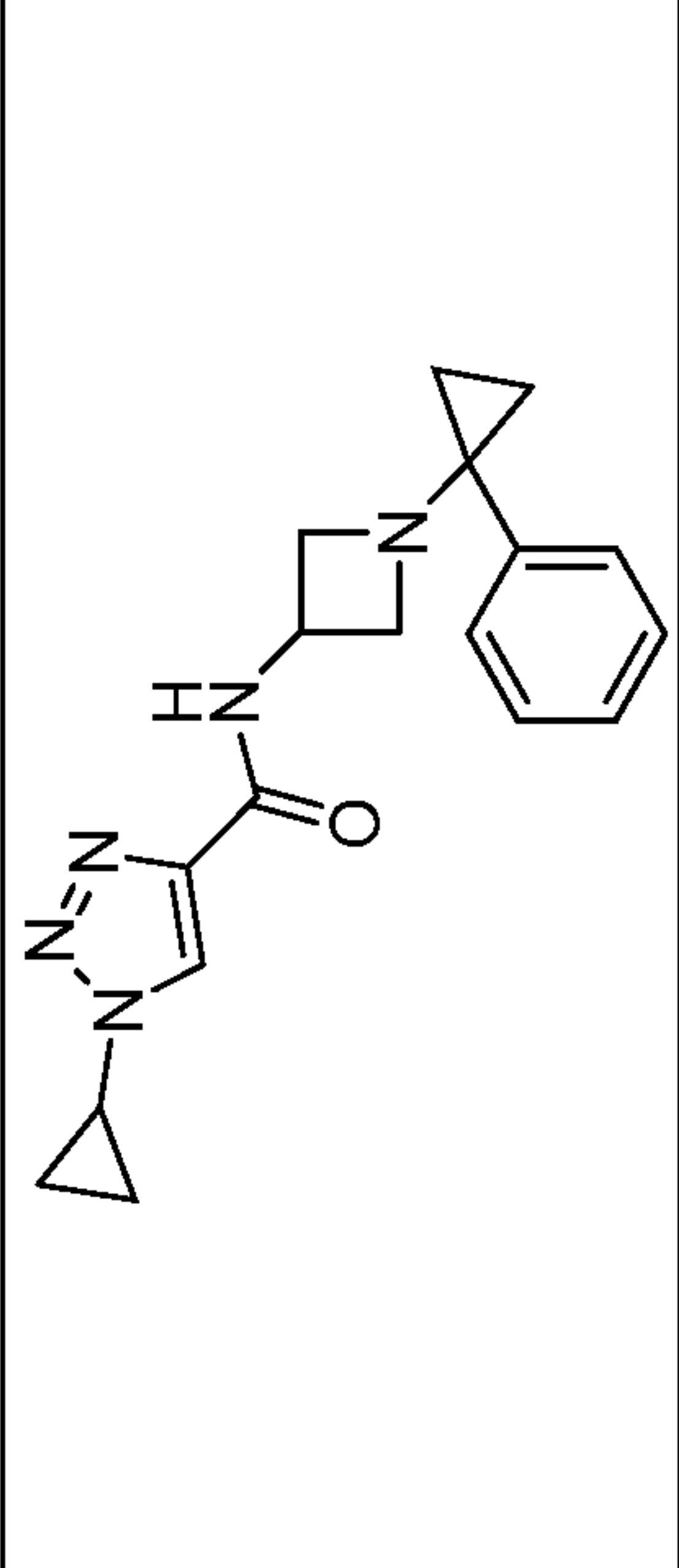
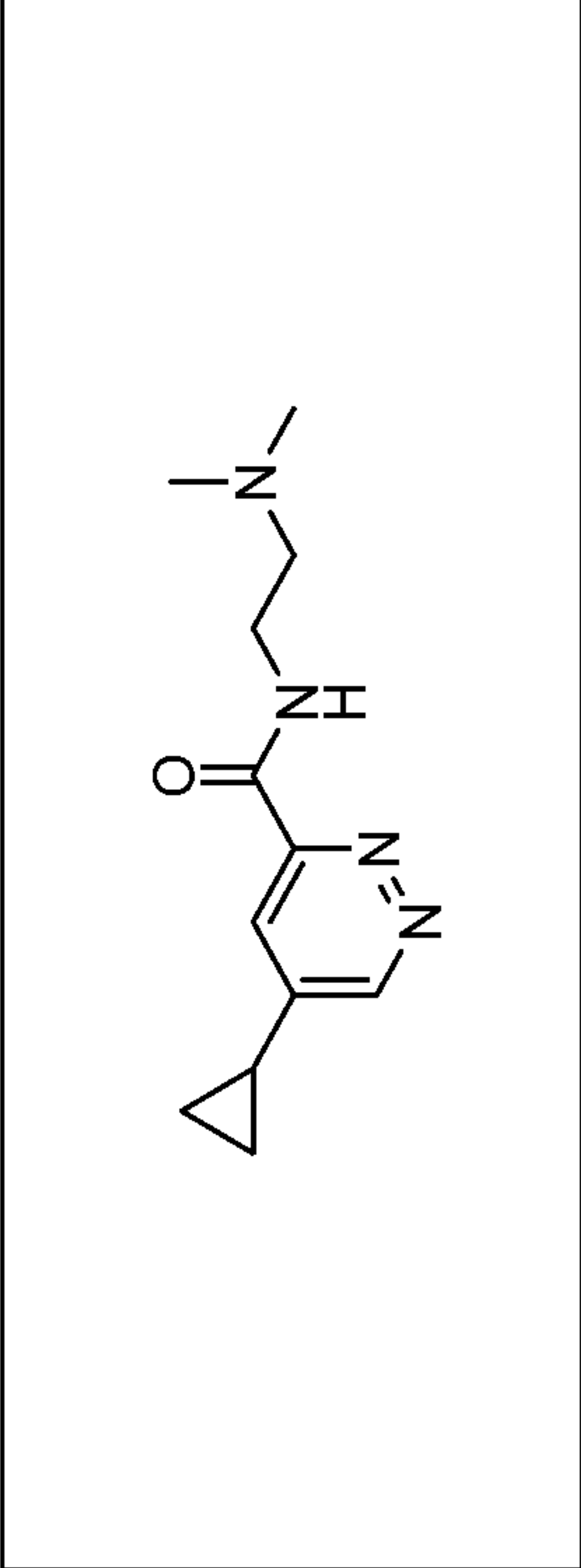
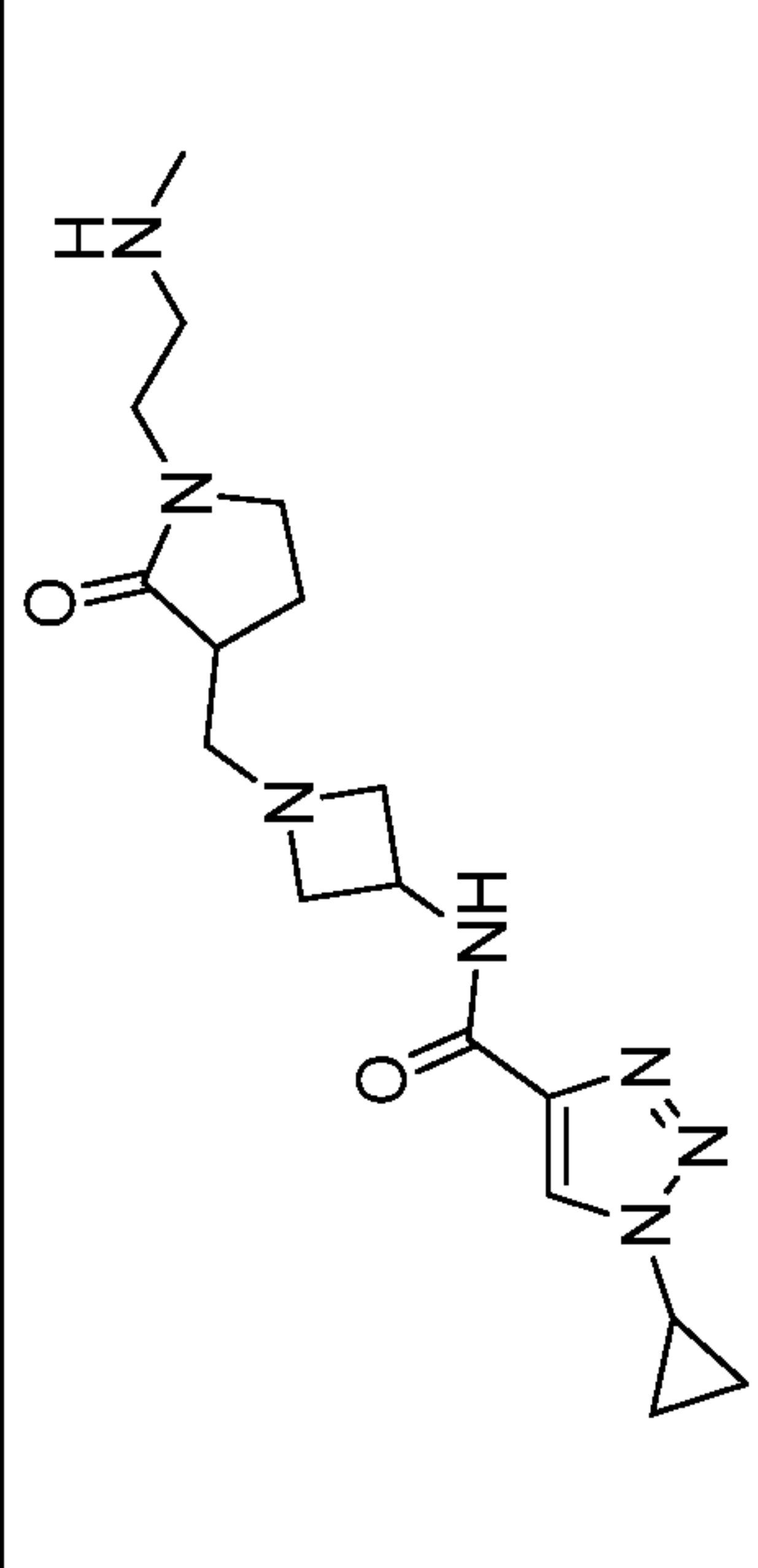
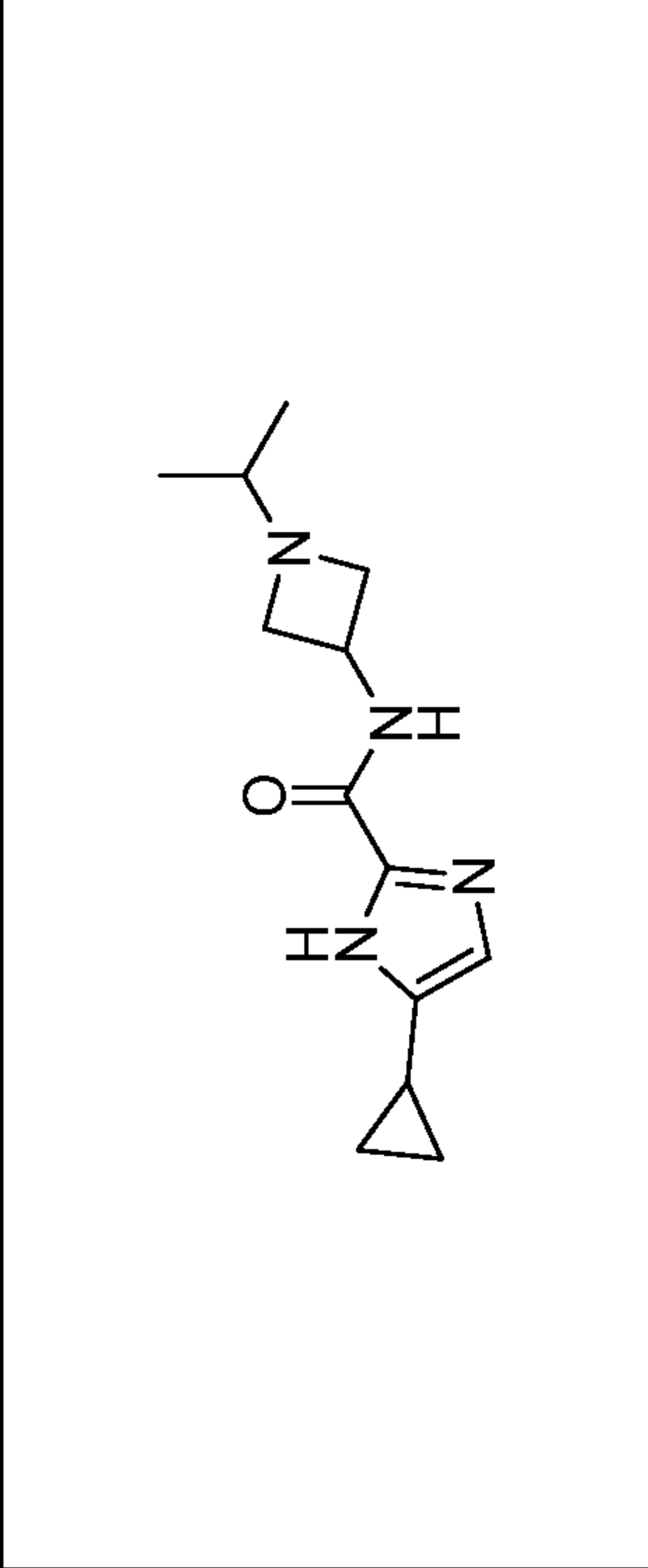
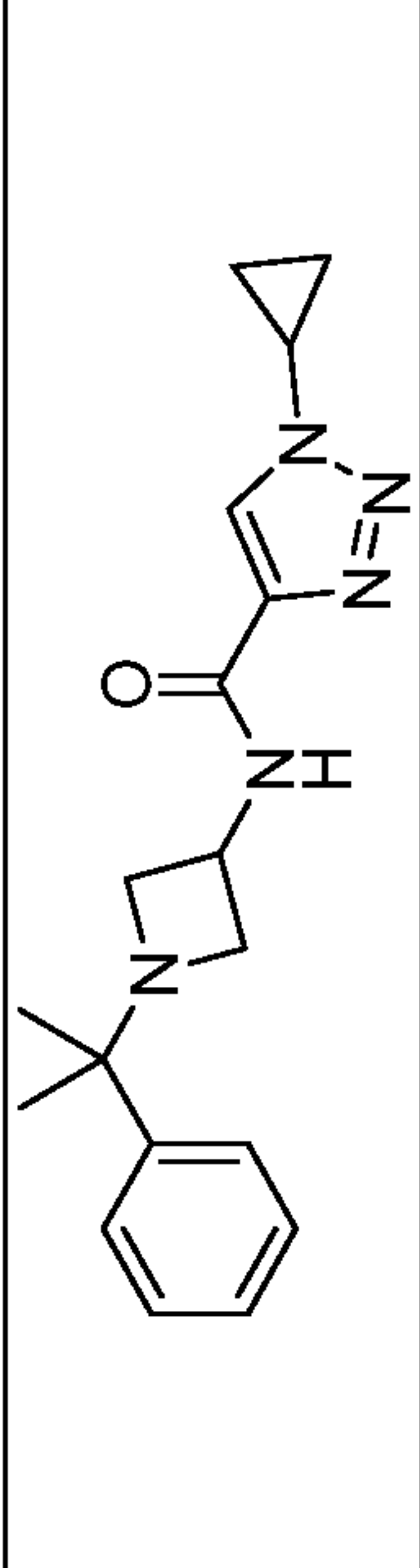
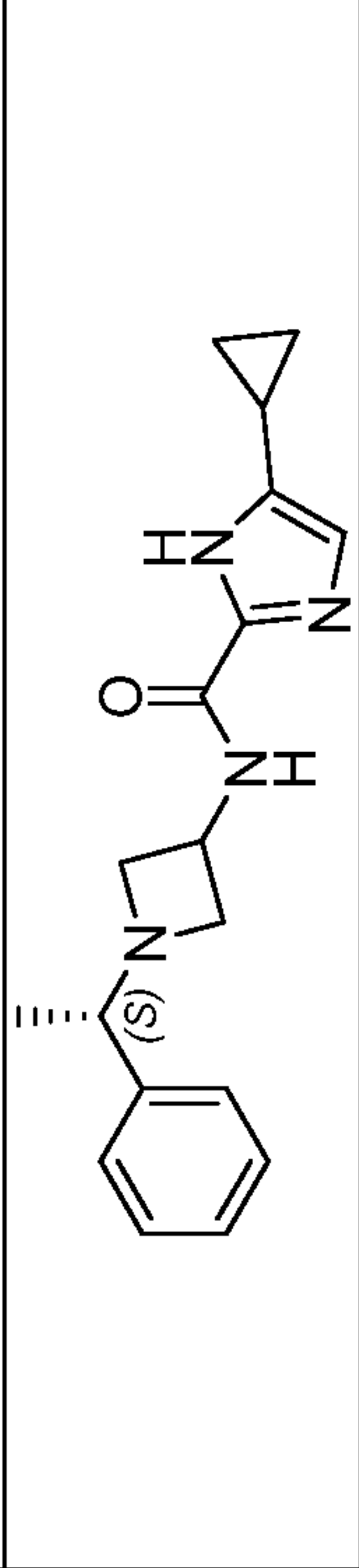
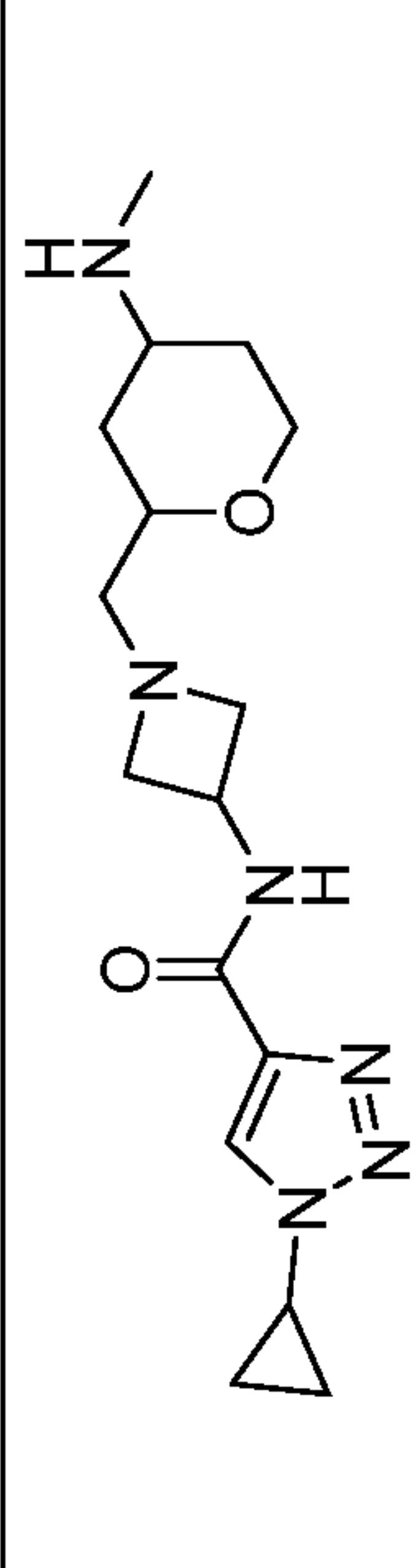
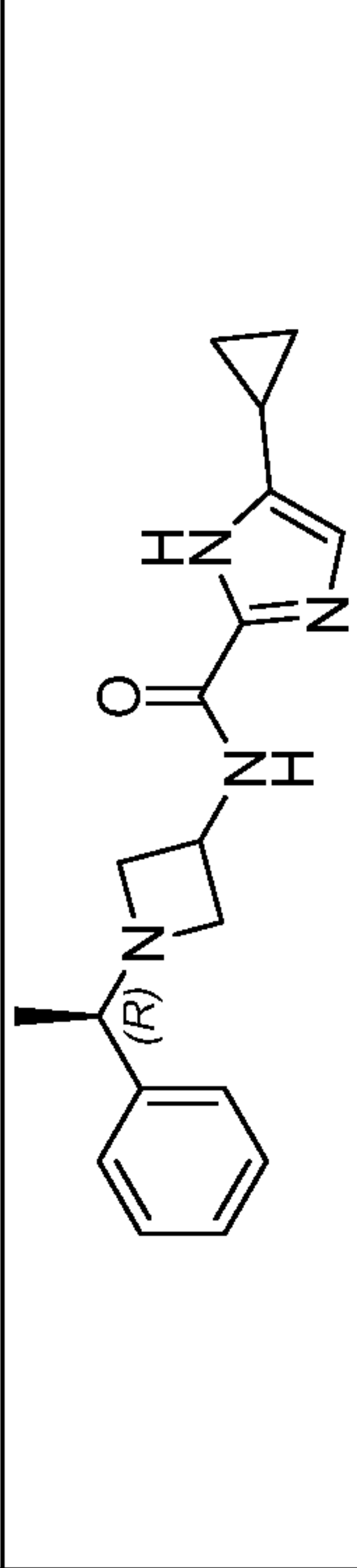
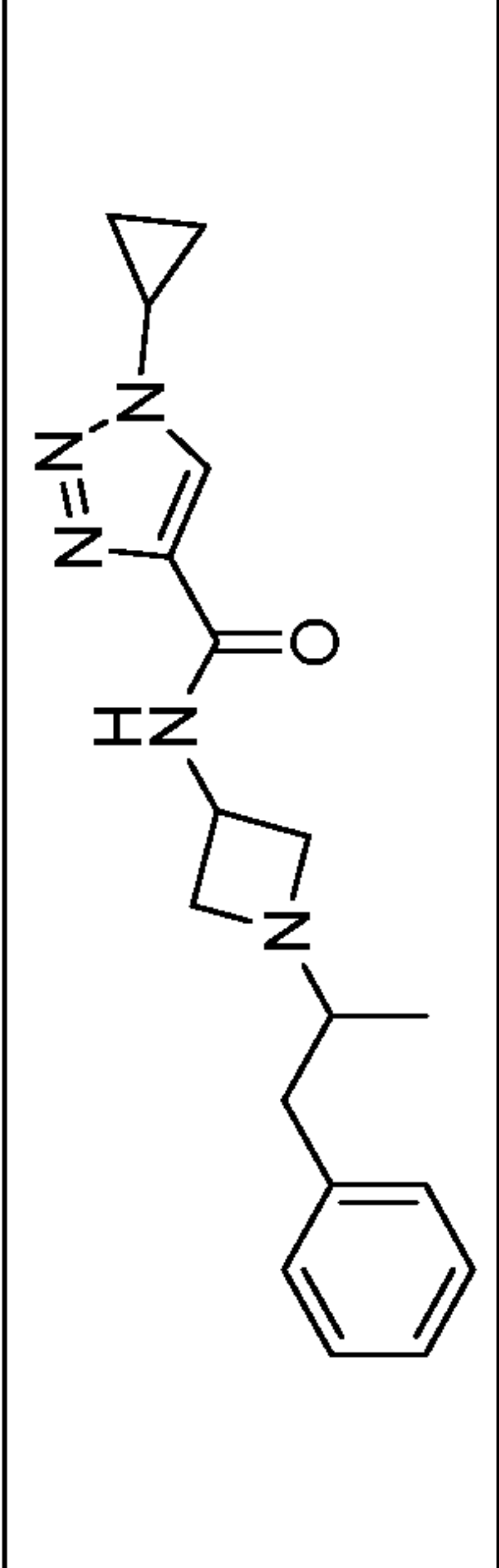
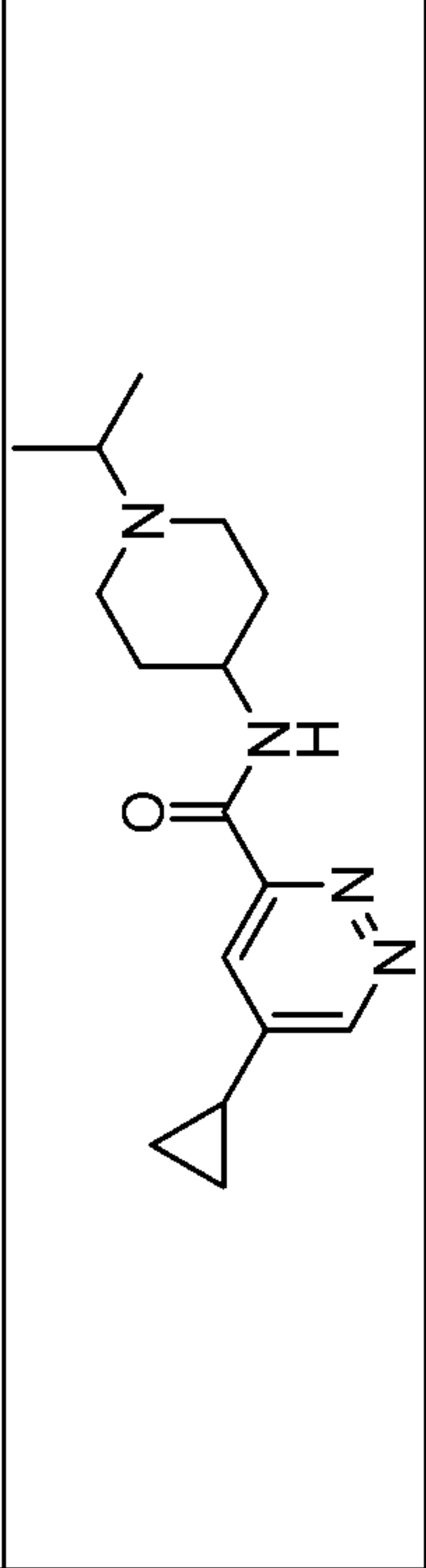
733		None	847		None
734		None	848		None
735		None	849		None
736		None	850		None
737		None	851		None

738		None	852		None
739		None	853		None
740		None	854		None
741		None	855		None

742		None	856		None
743		None	857		None
744		None	858		None
745		None	859		None
746		None	860		None

747		None	861		None
748		None	862		None
749		None	863		None
750		None	864		None

751		None	865		None
752		None	866		None
753		None	867		None
754		None	868		None

755		None	869		None
756		None	913		None
757		None	914		None
758		None	915		None
759		None	916		None

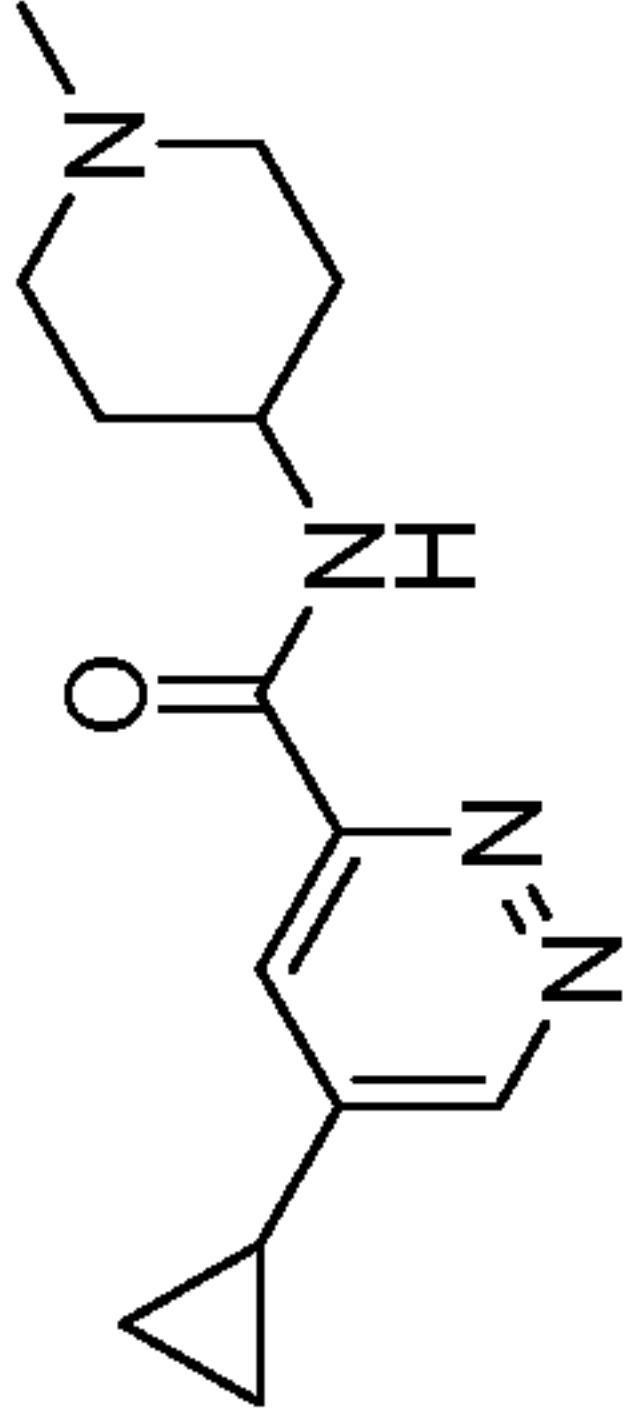
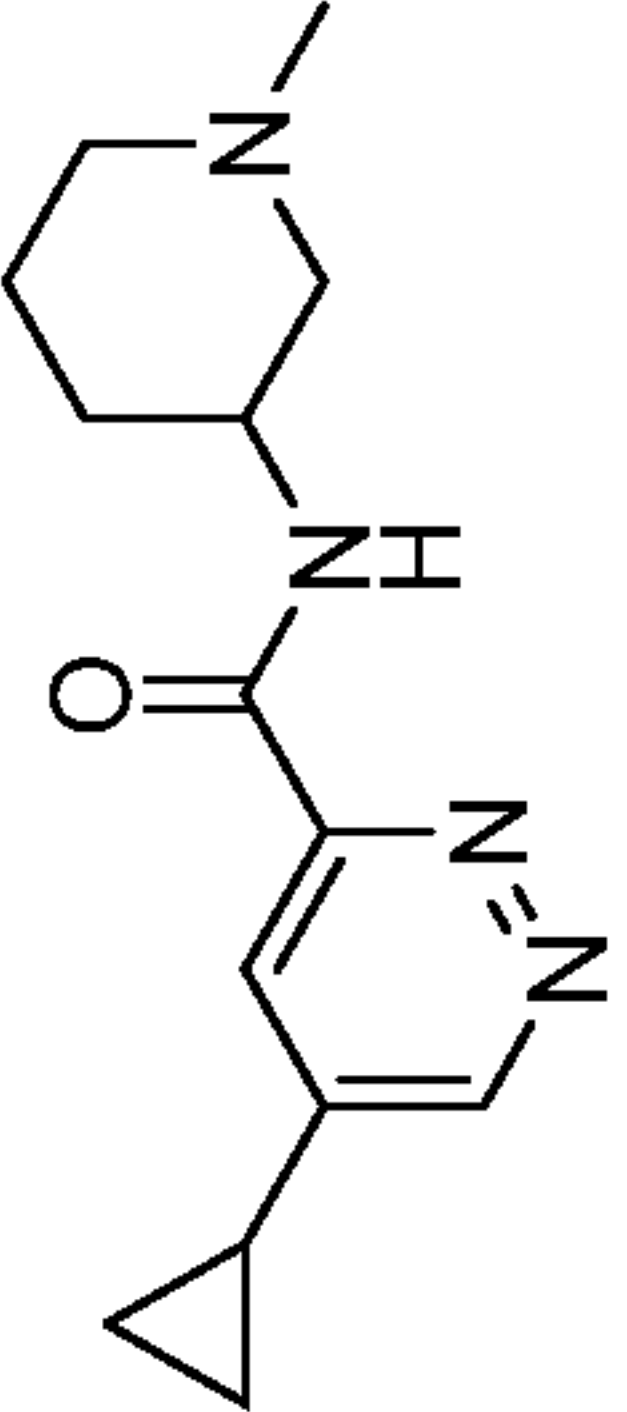
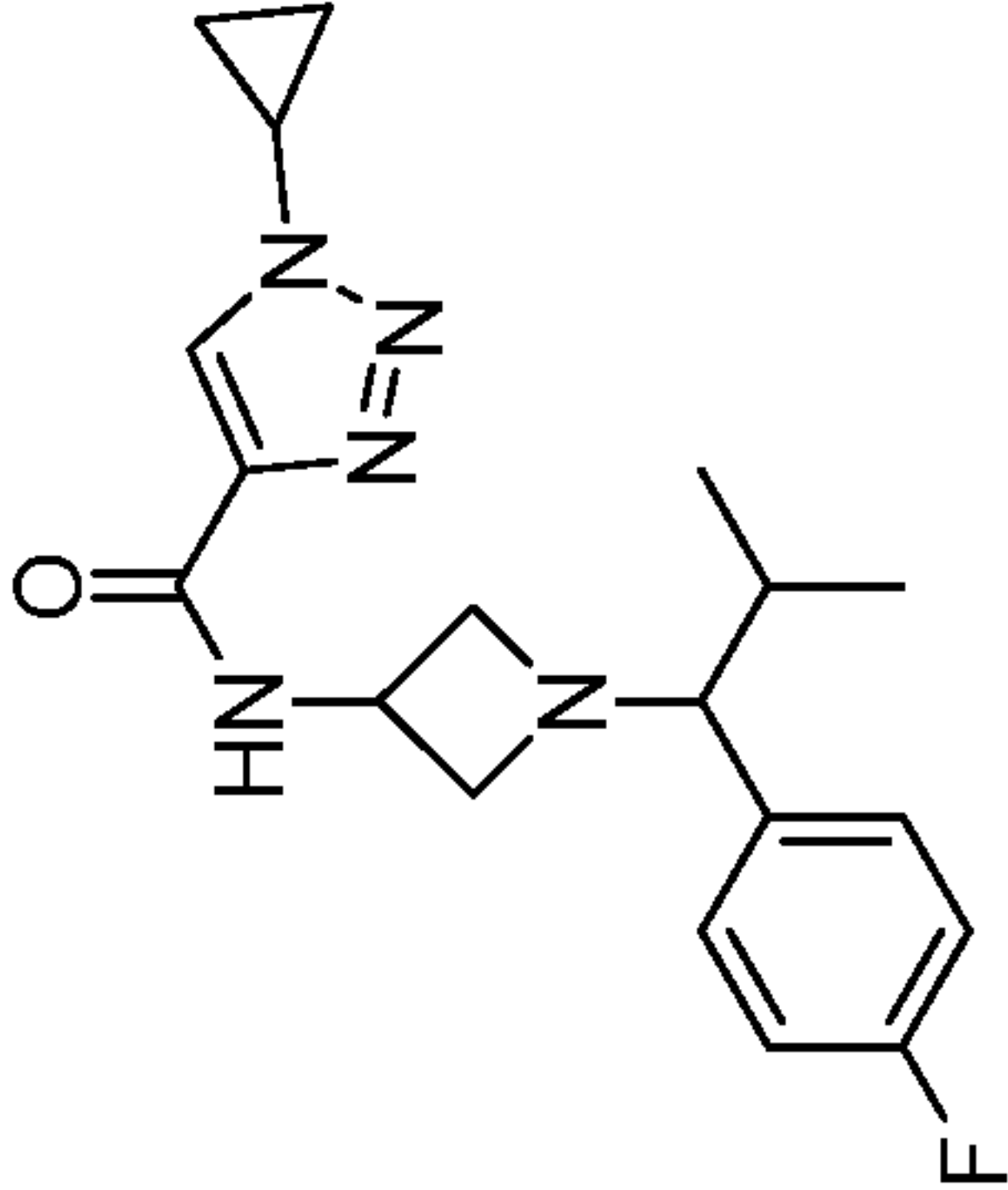
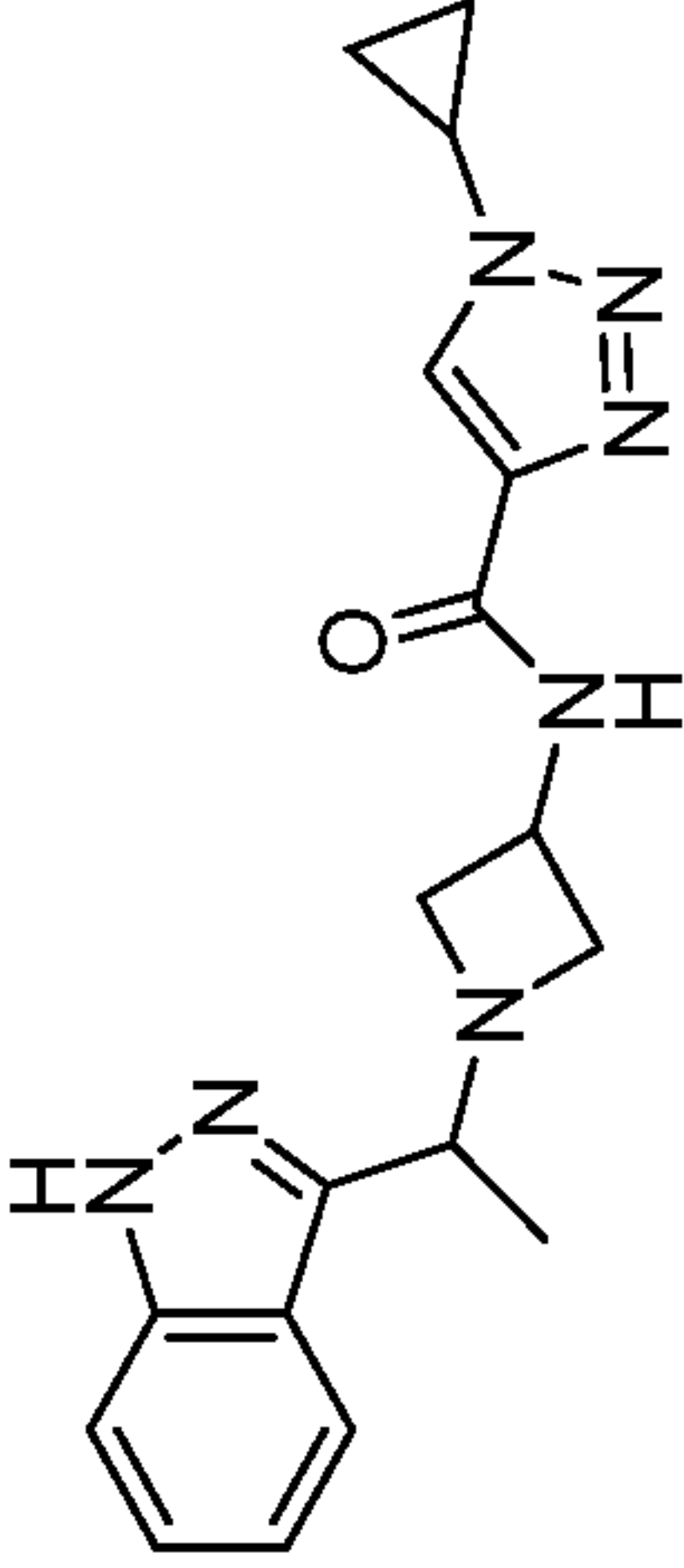
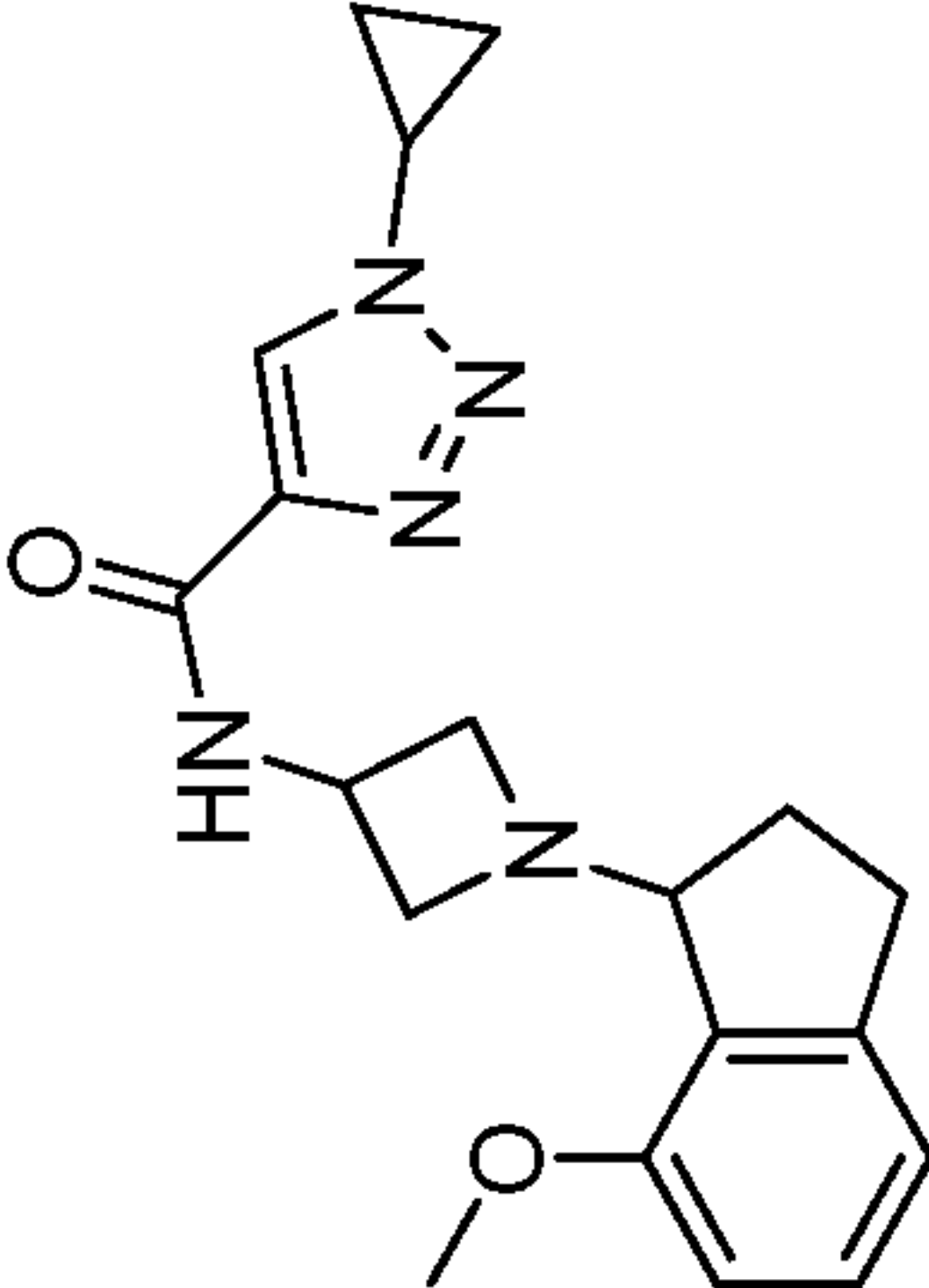
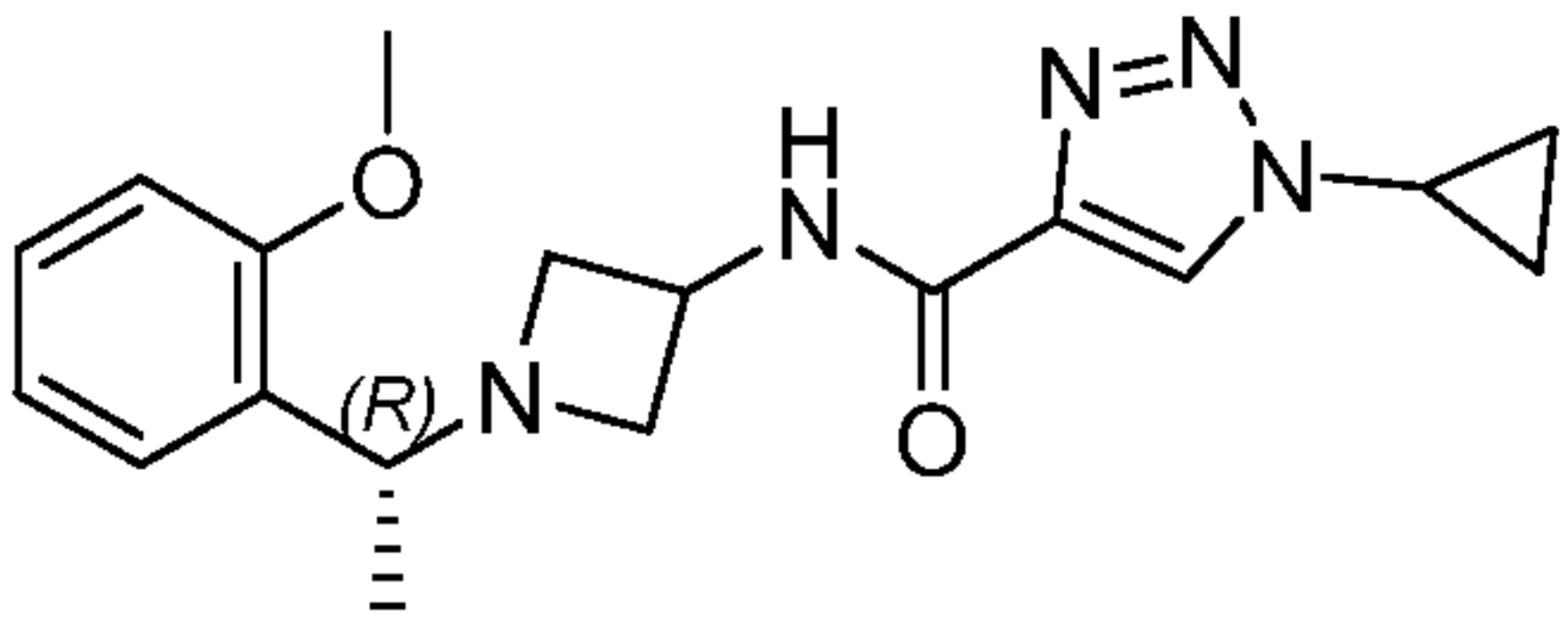
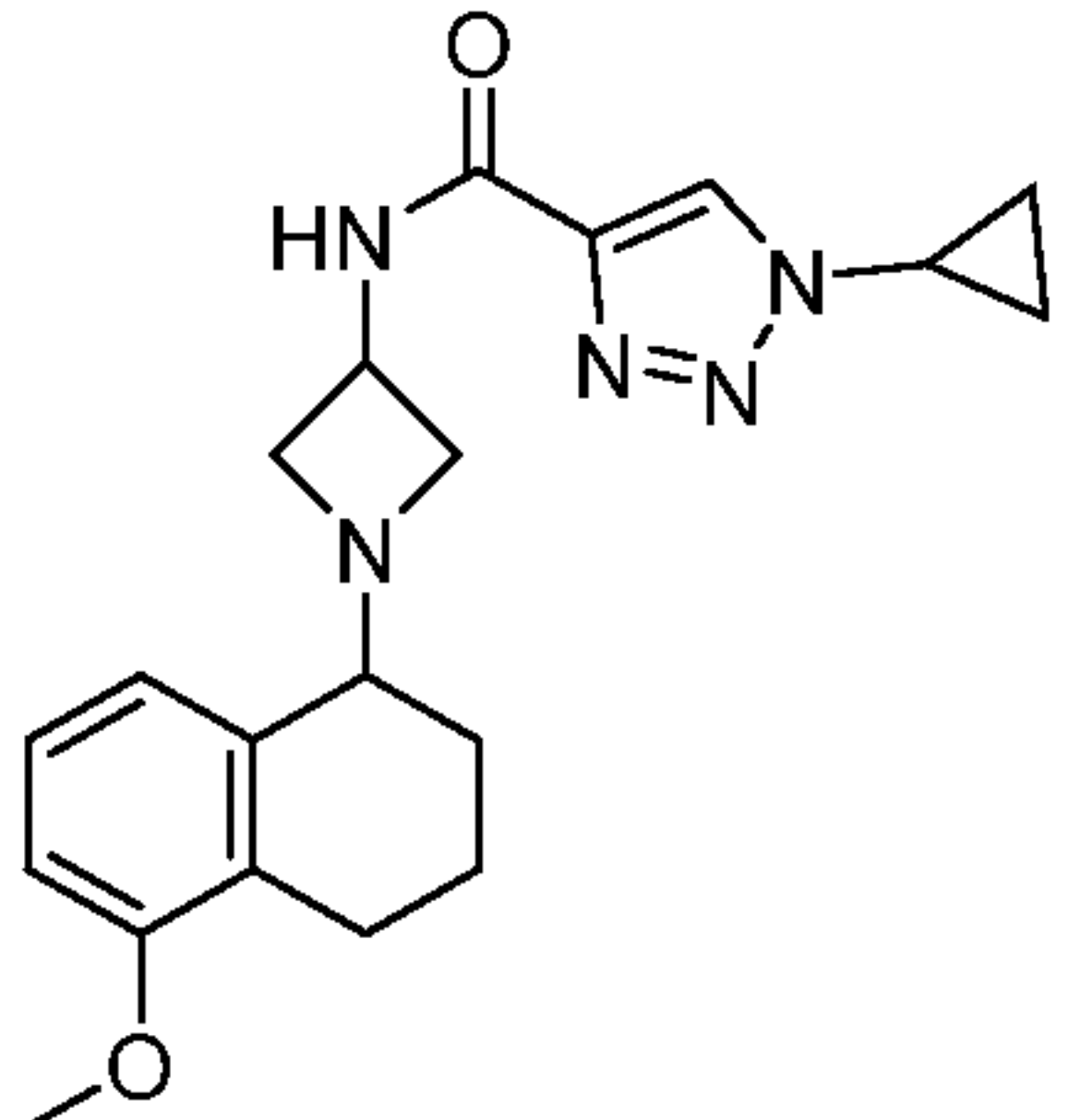
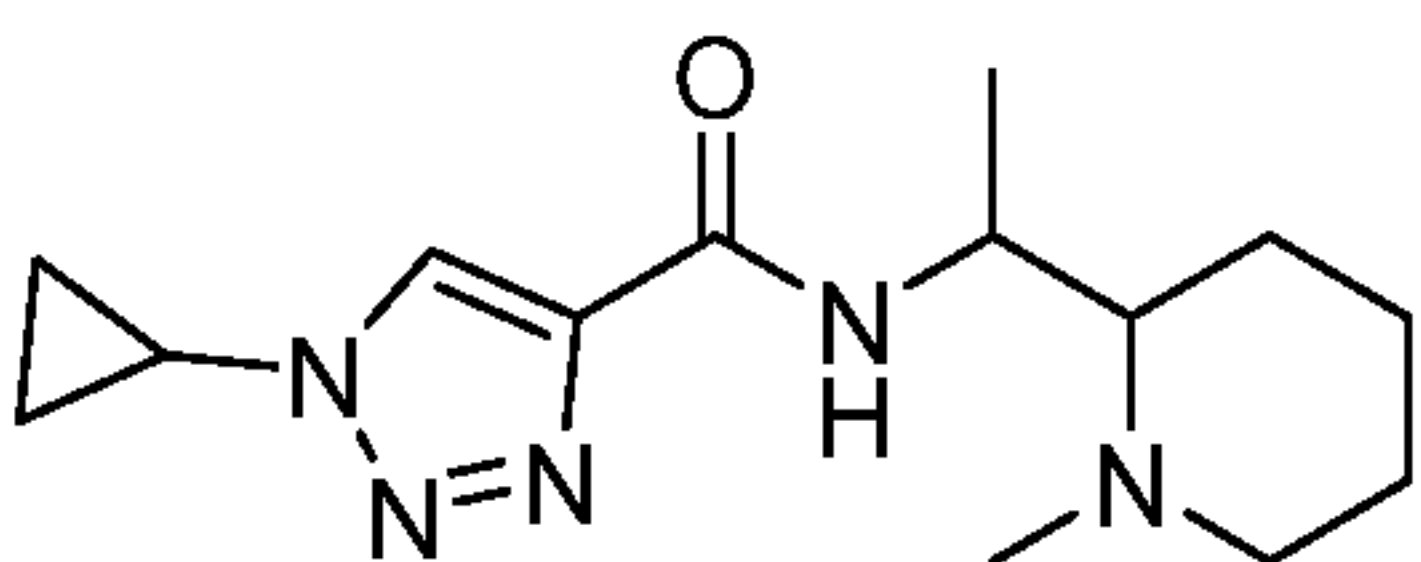
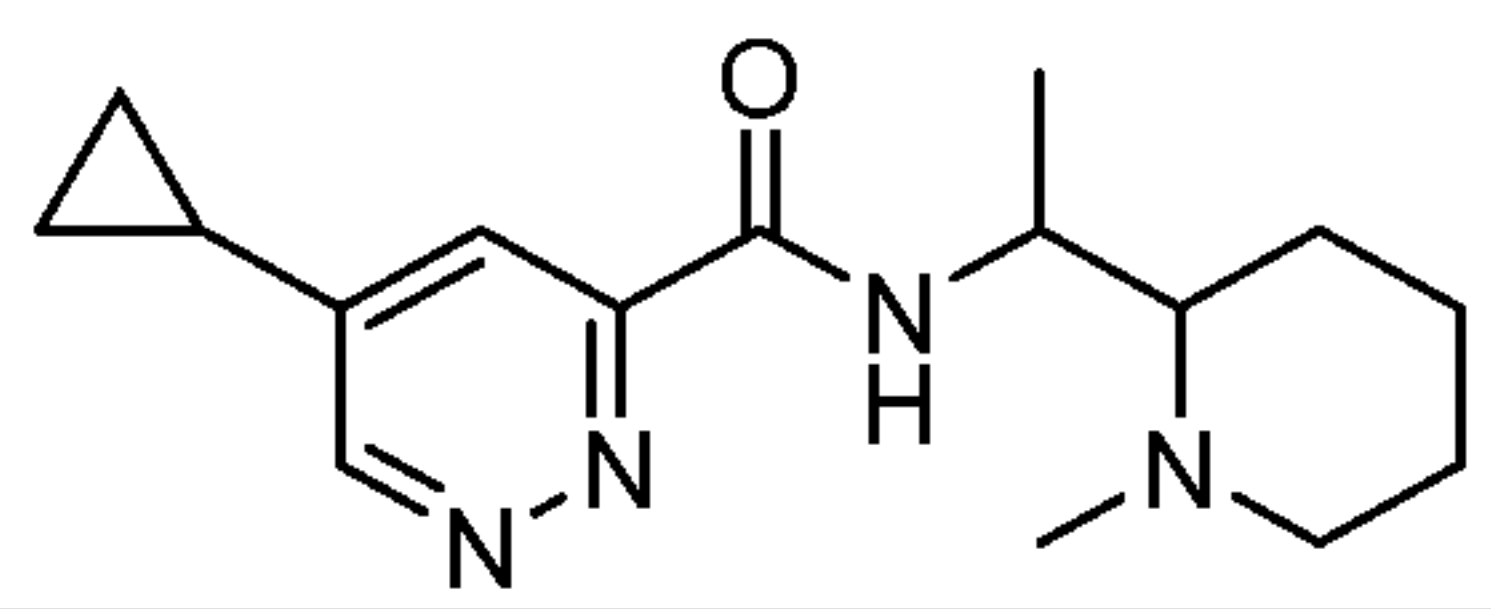
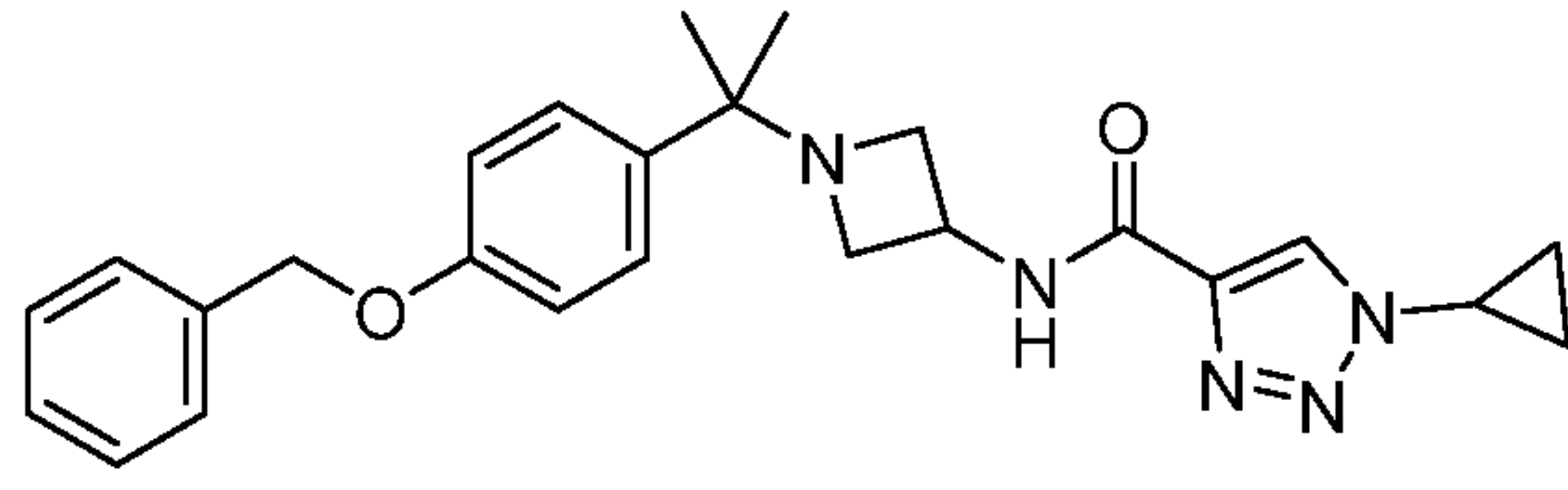
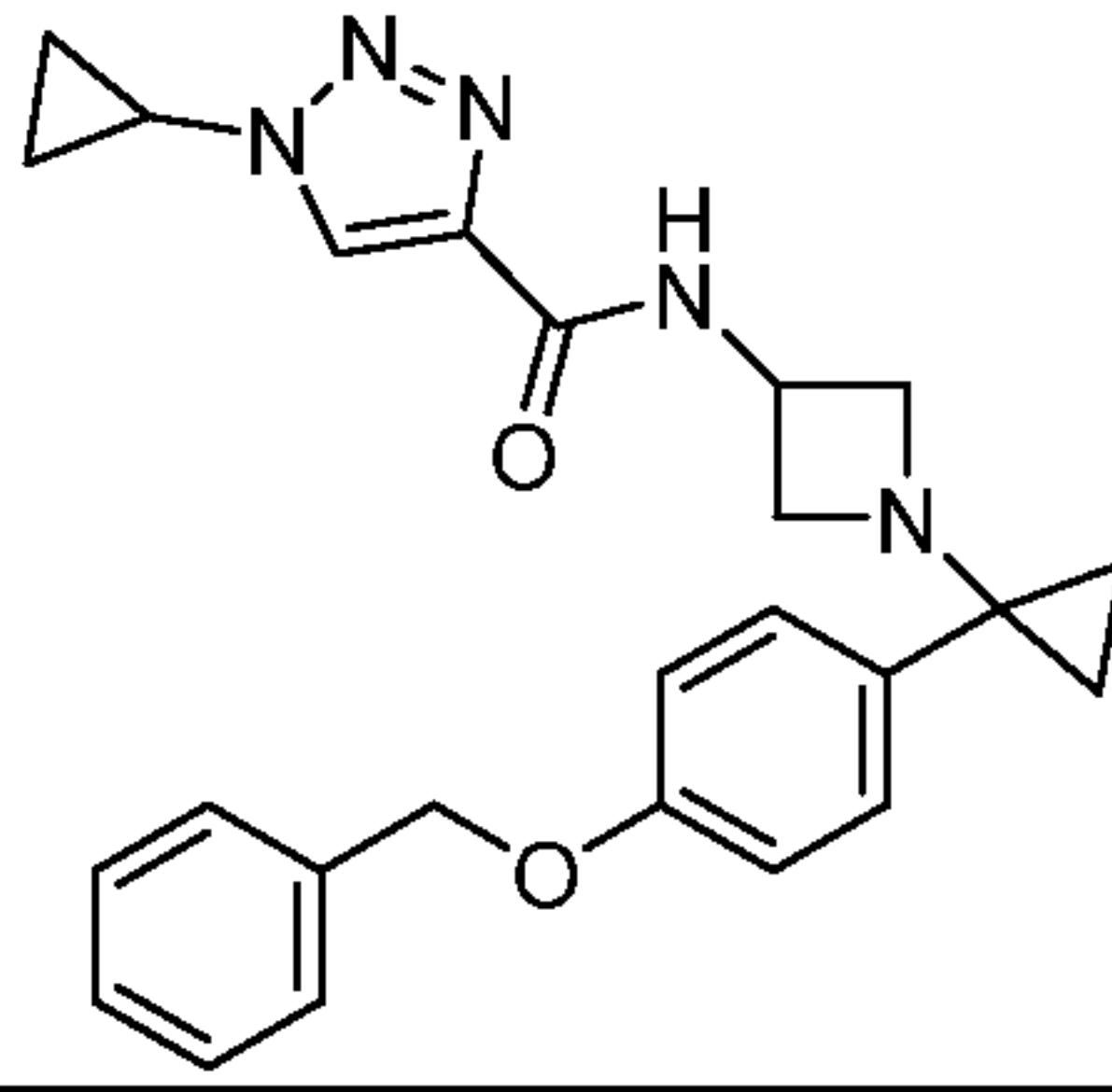
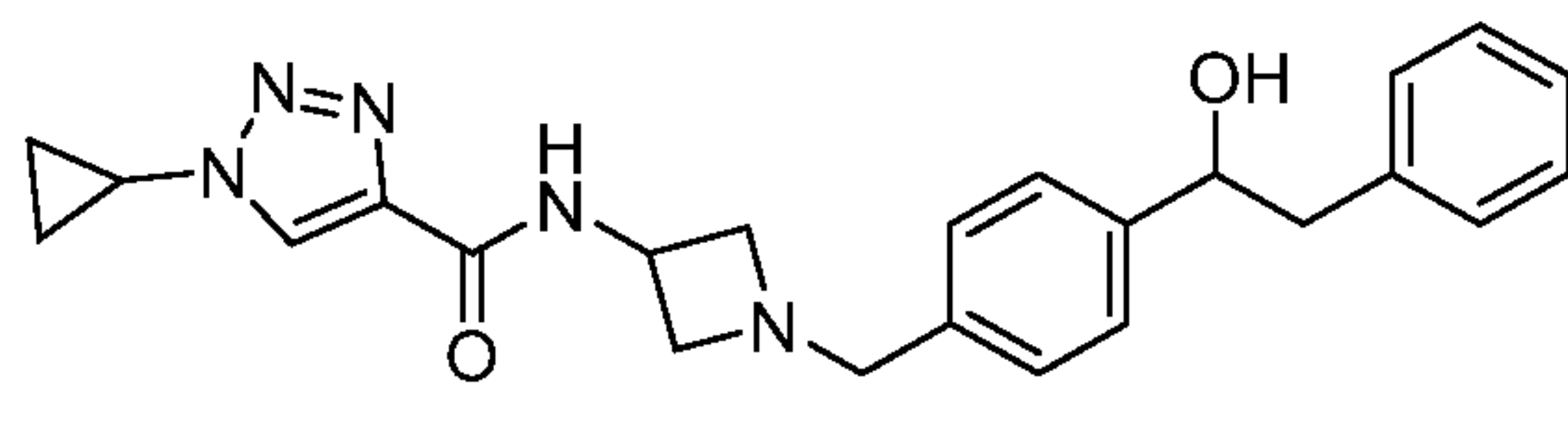
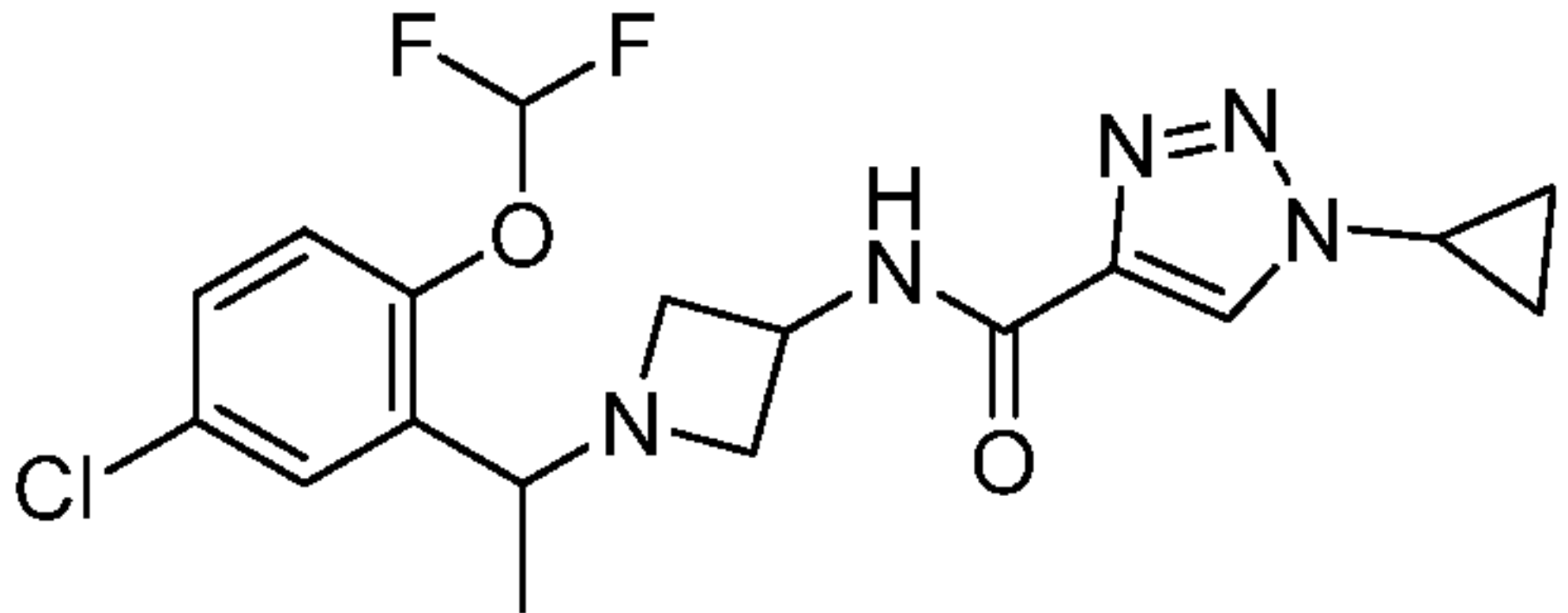
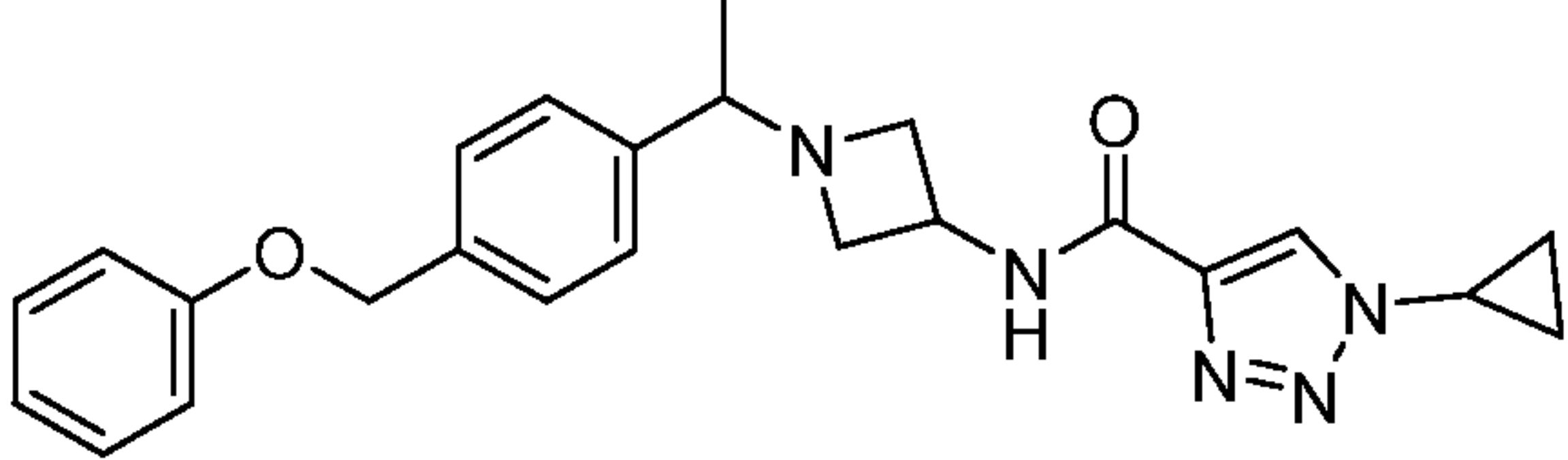
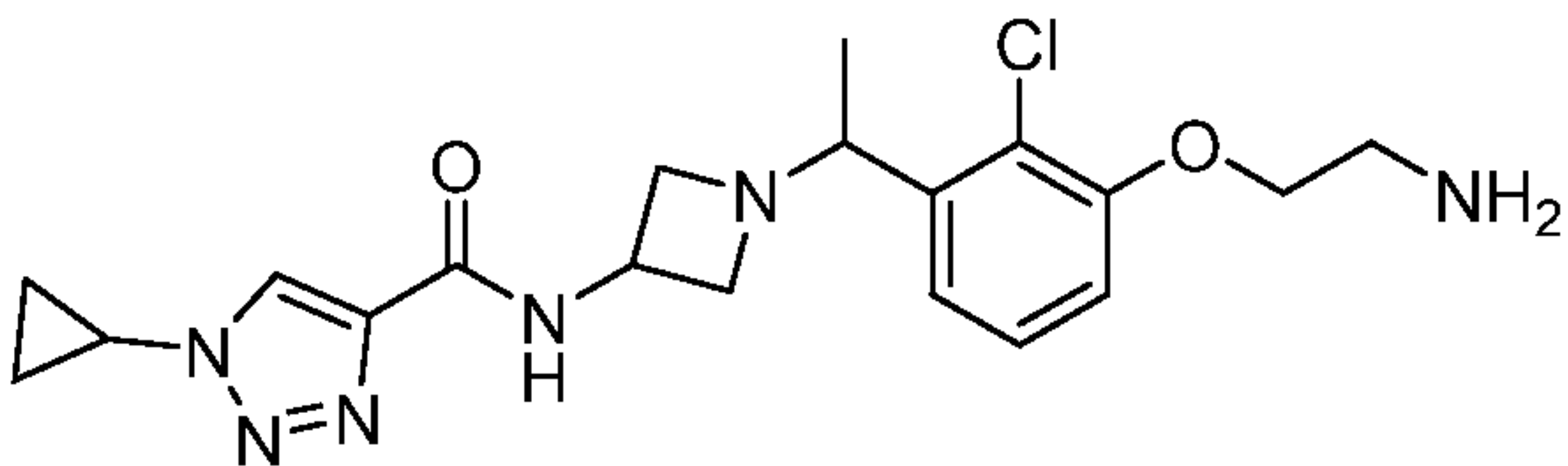
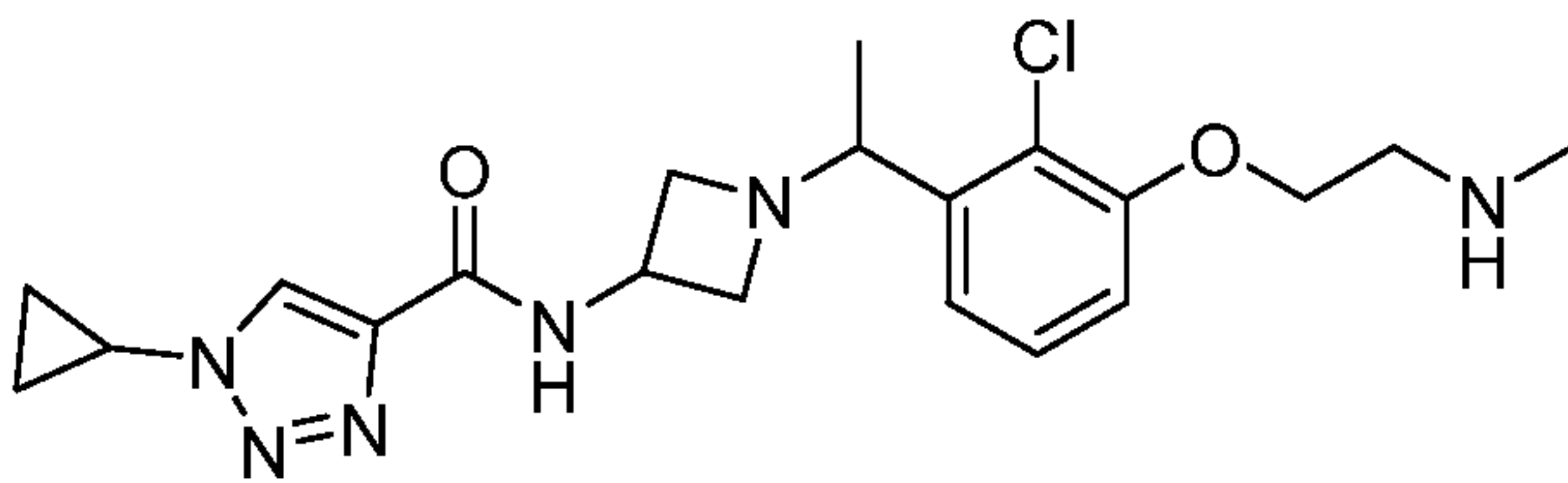
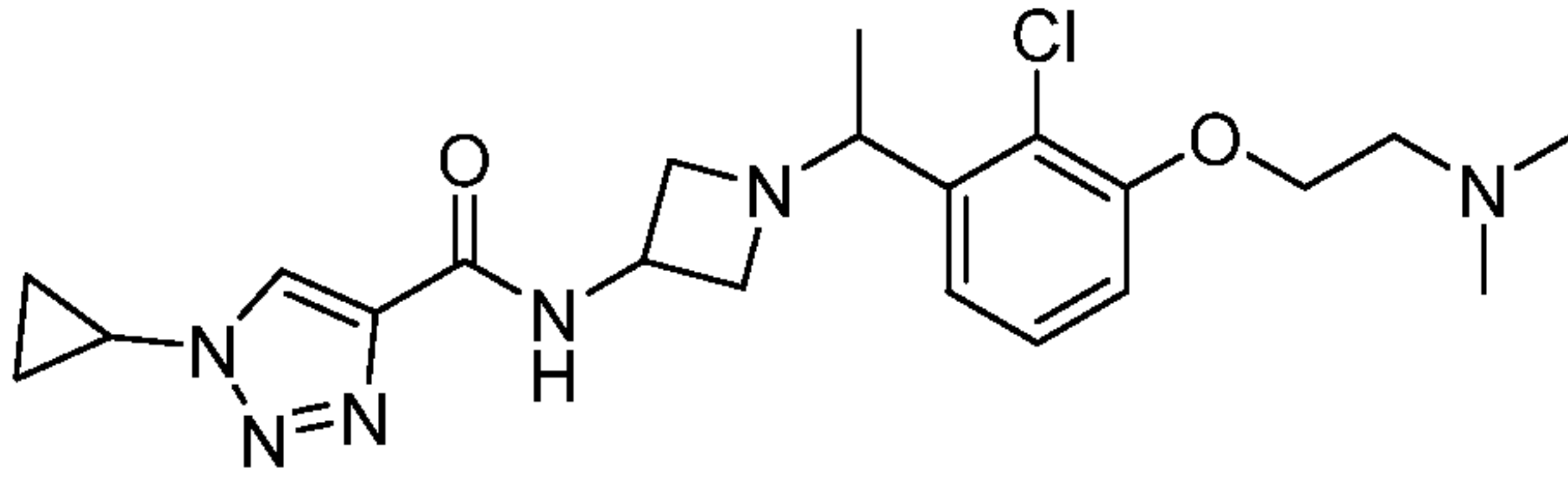
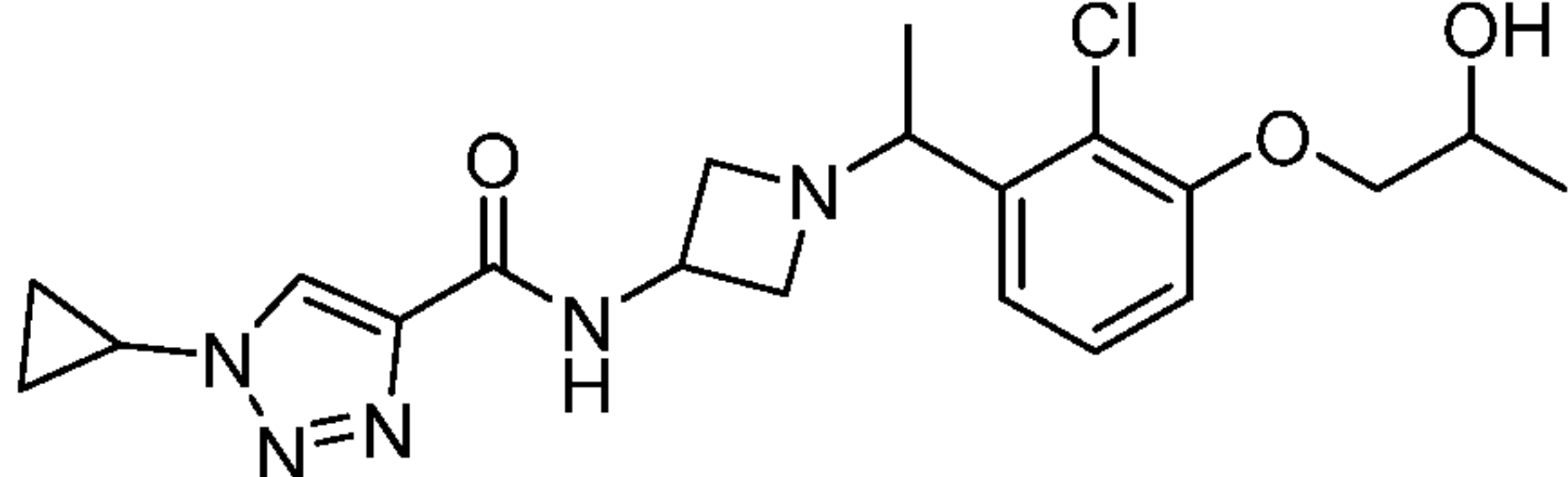
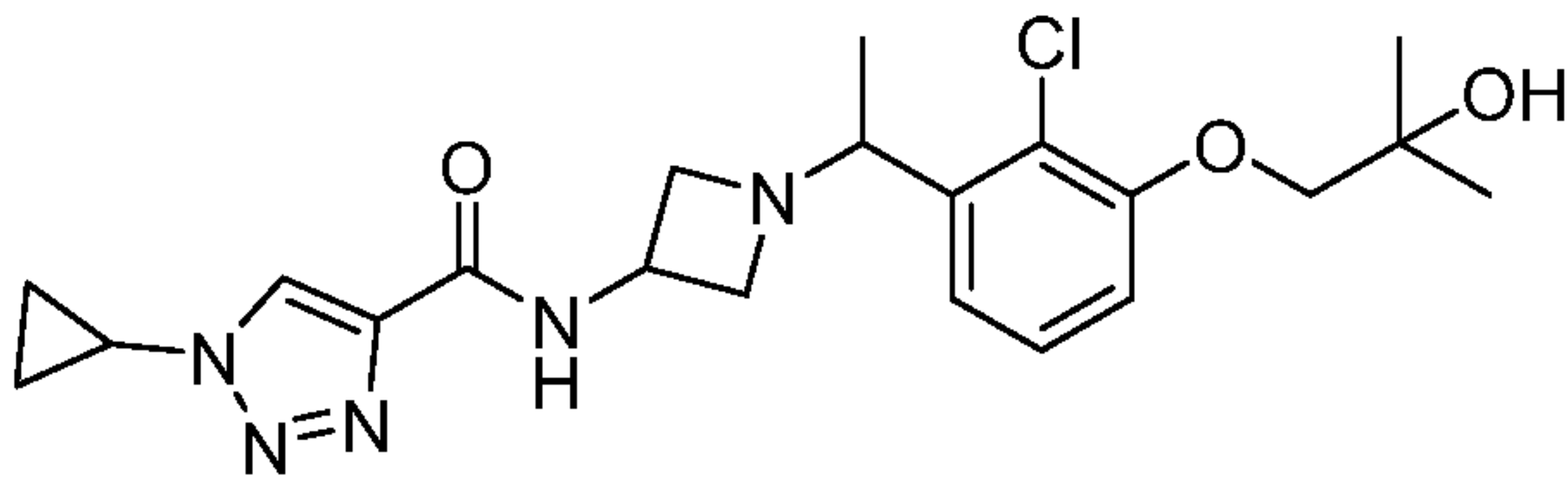
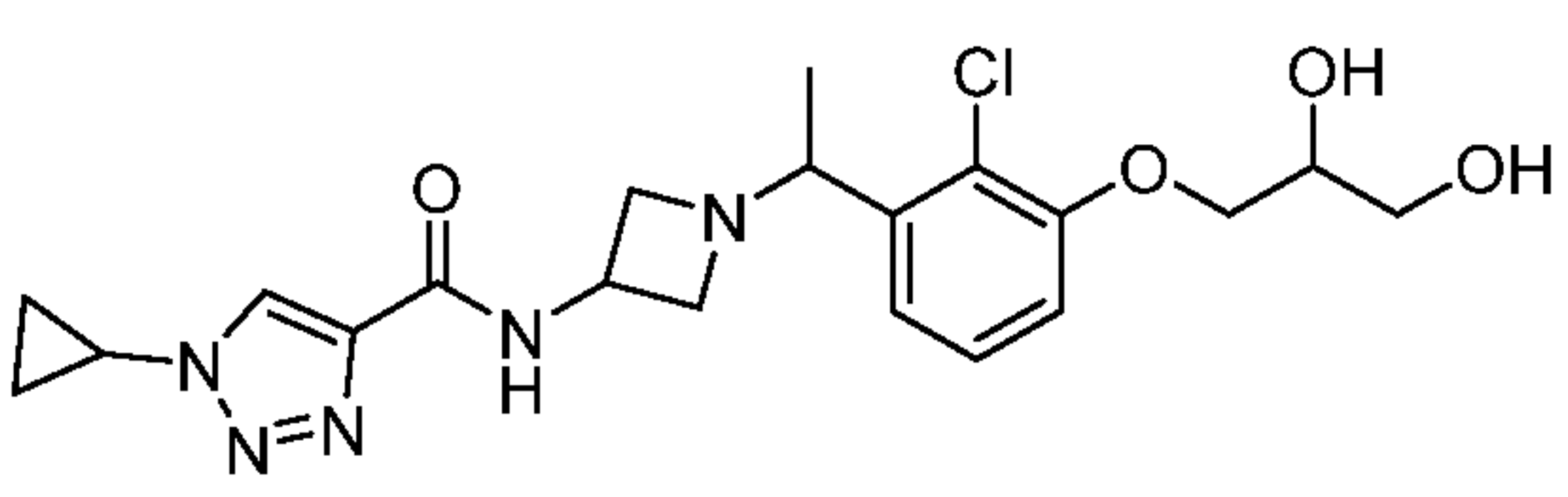
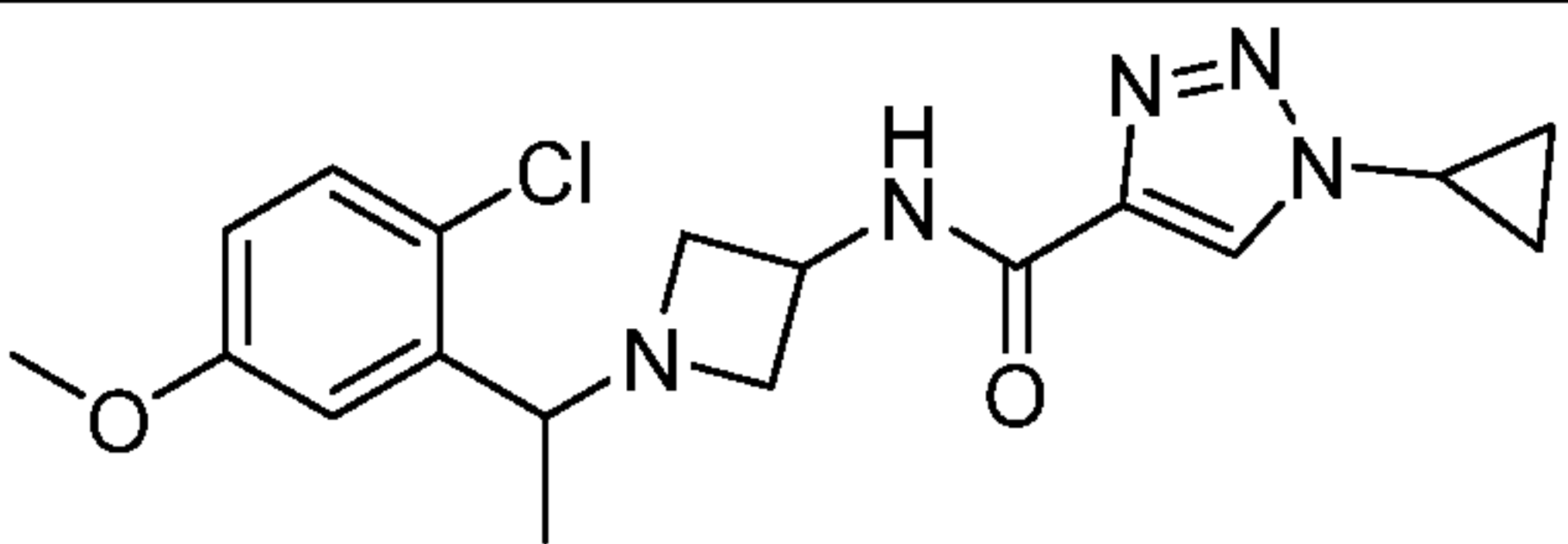
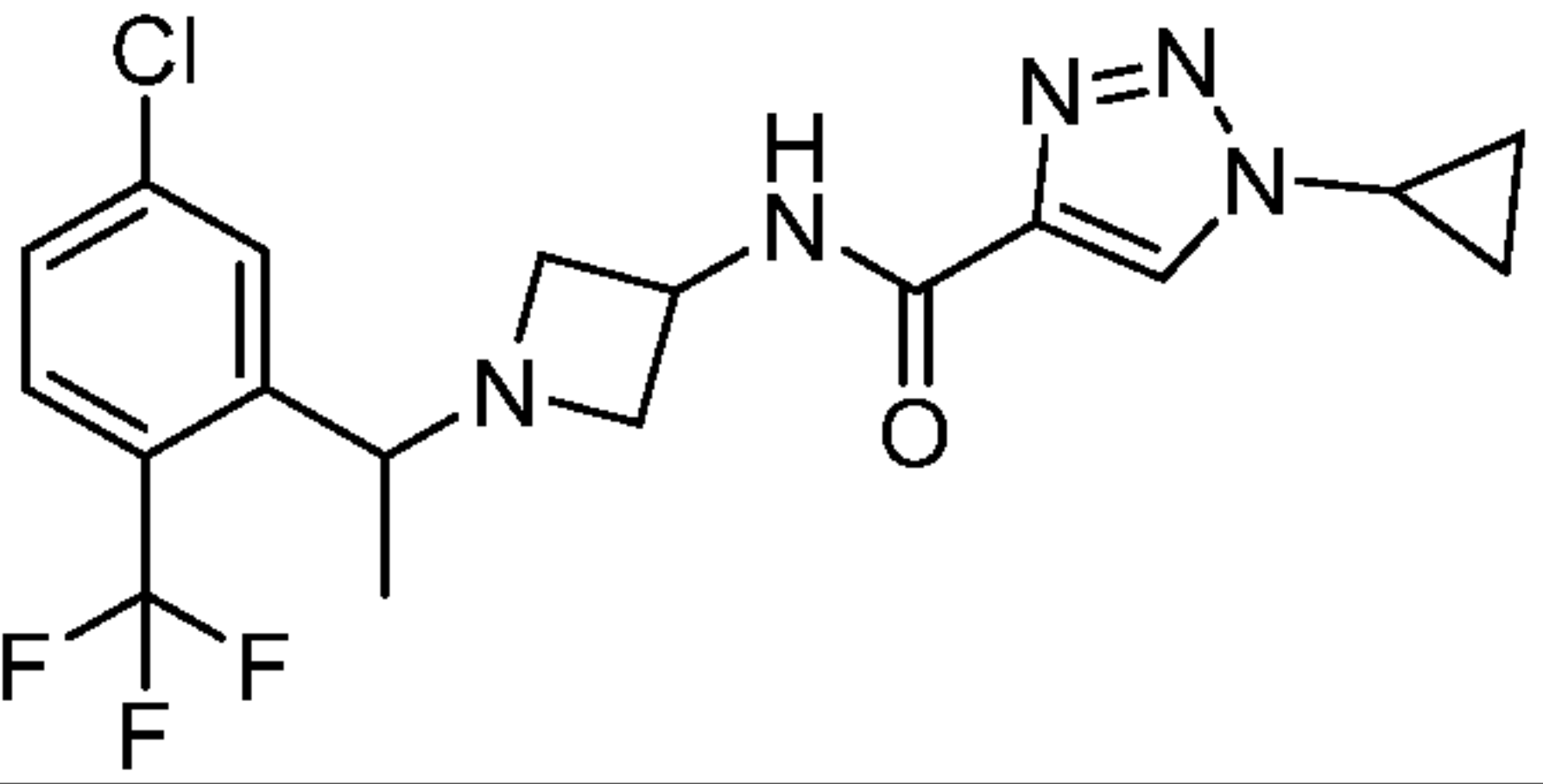
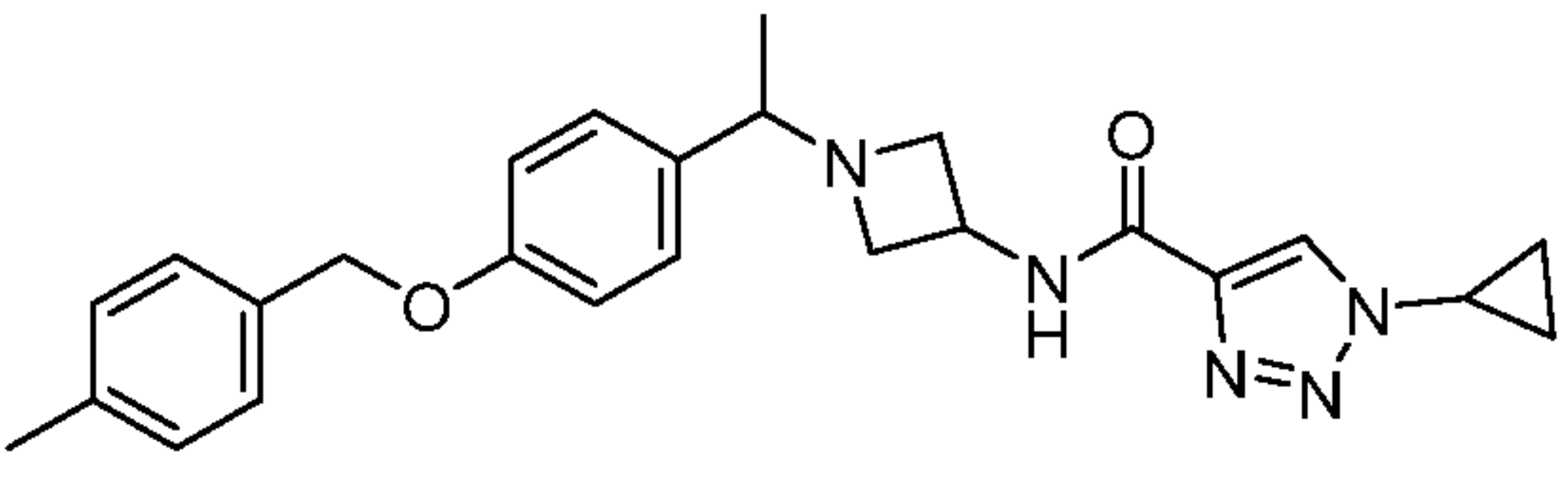
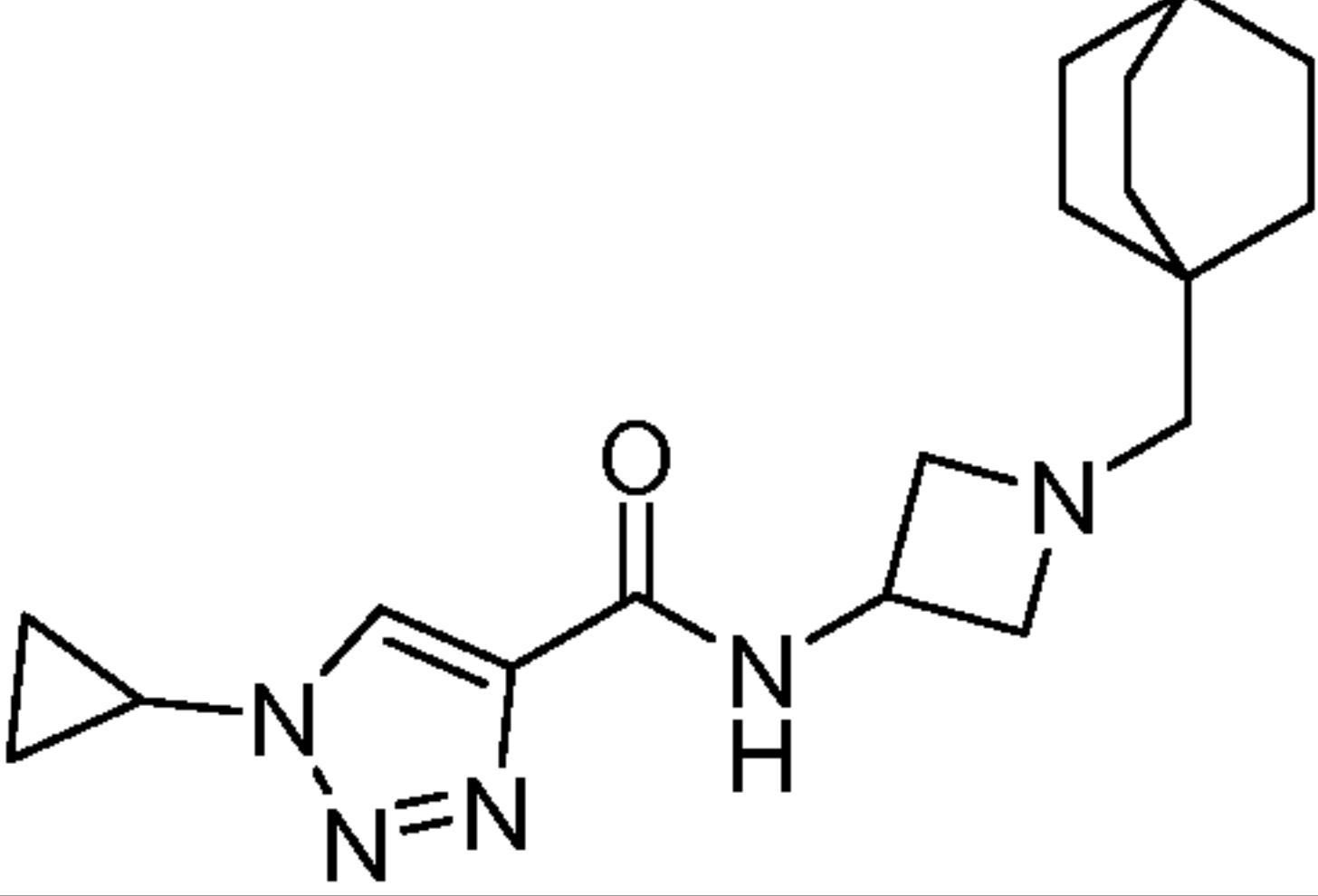
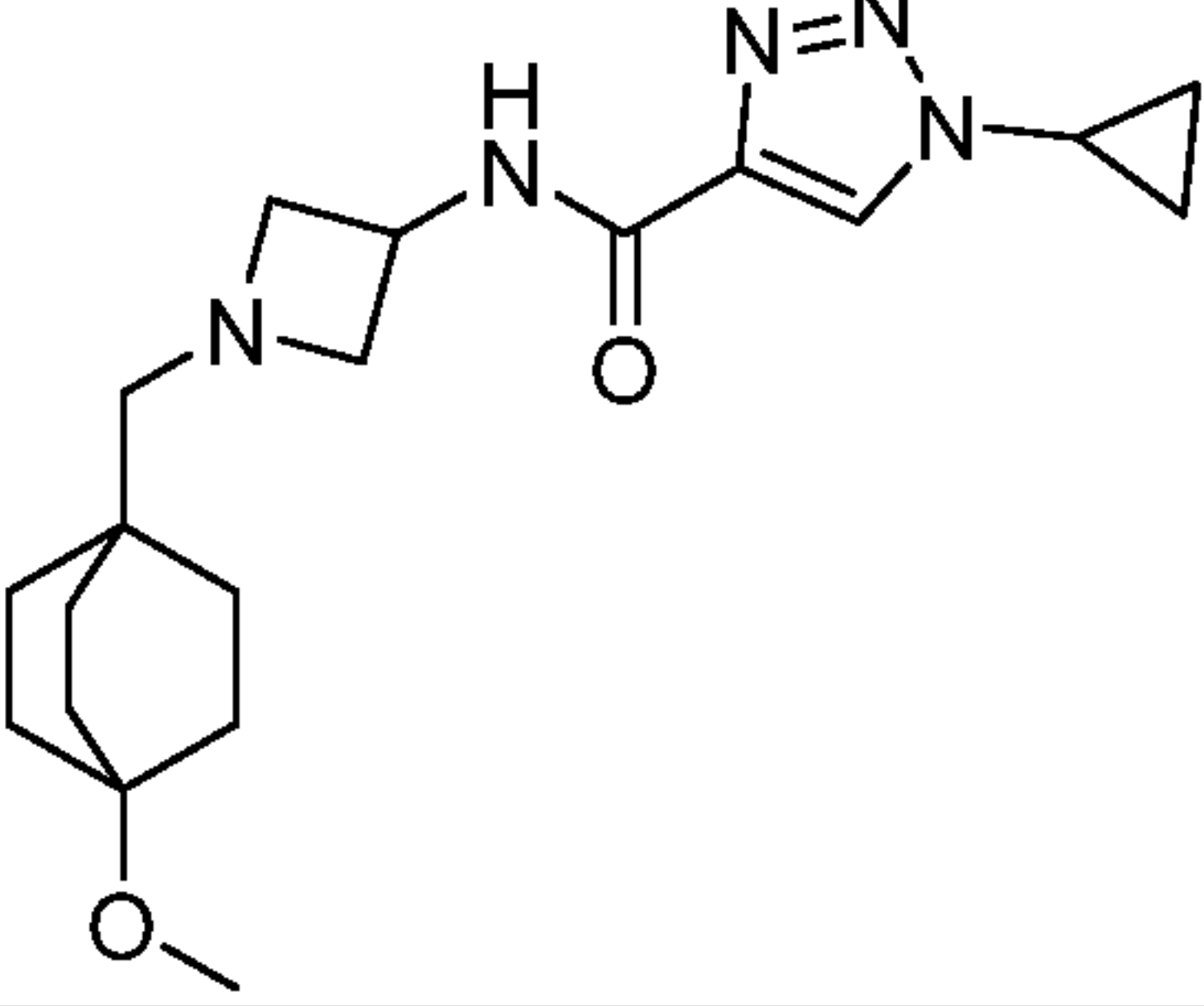
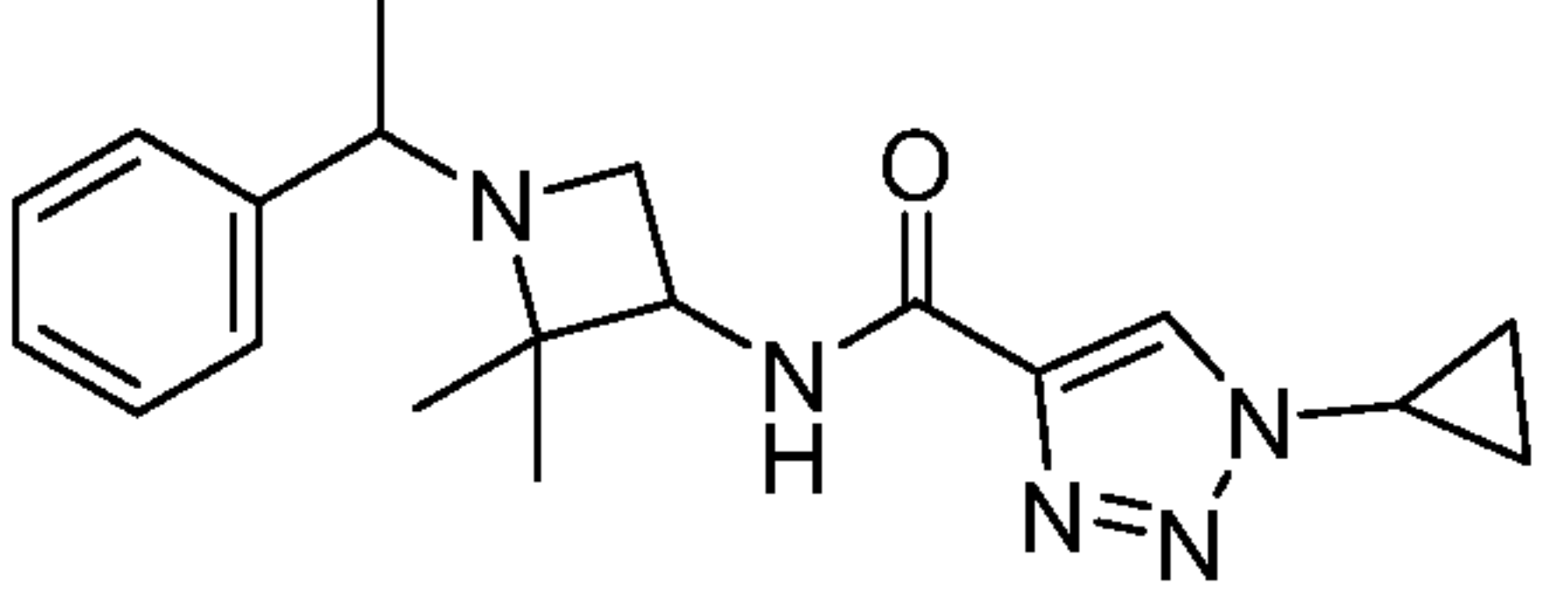
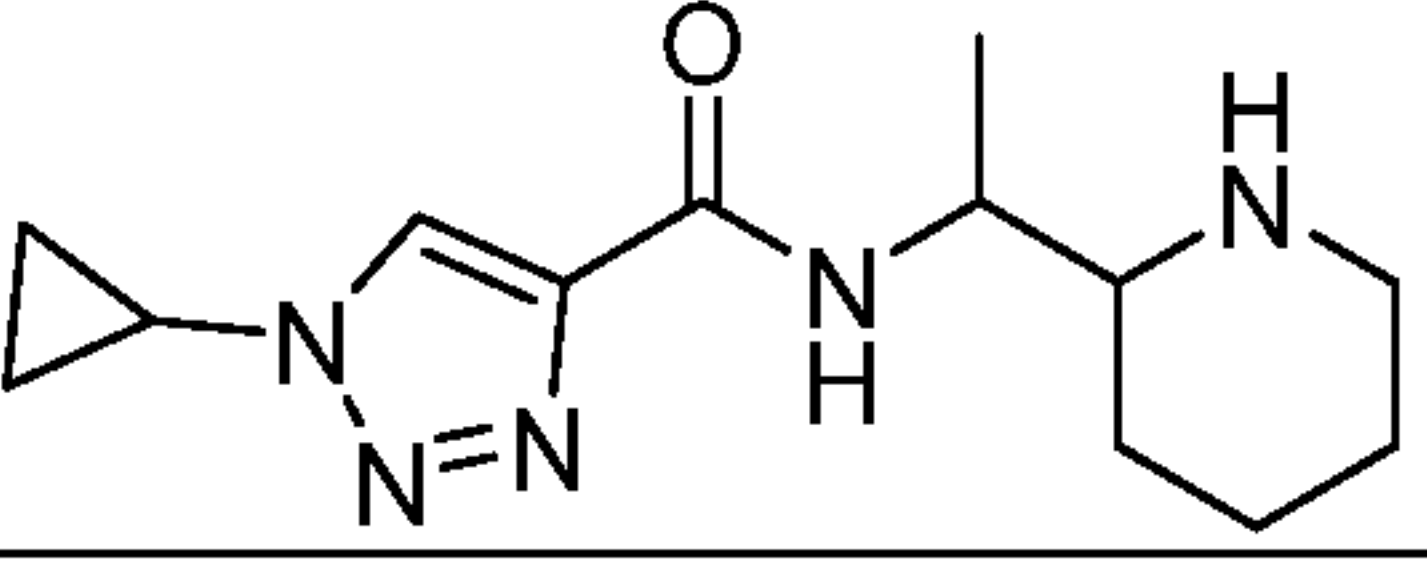
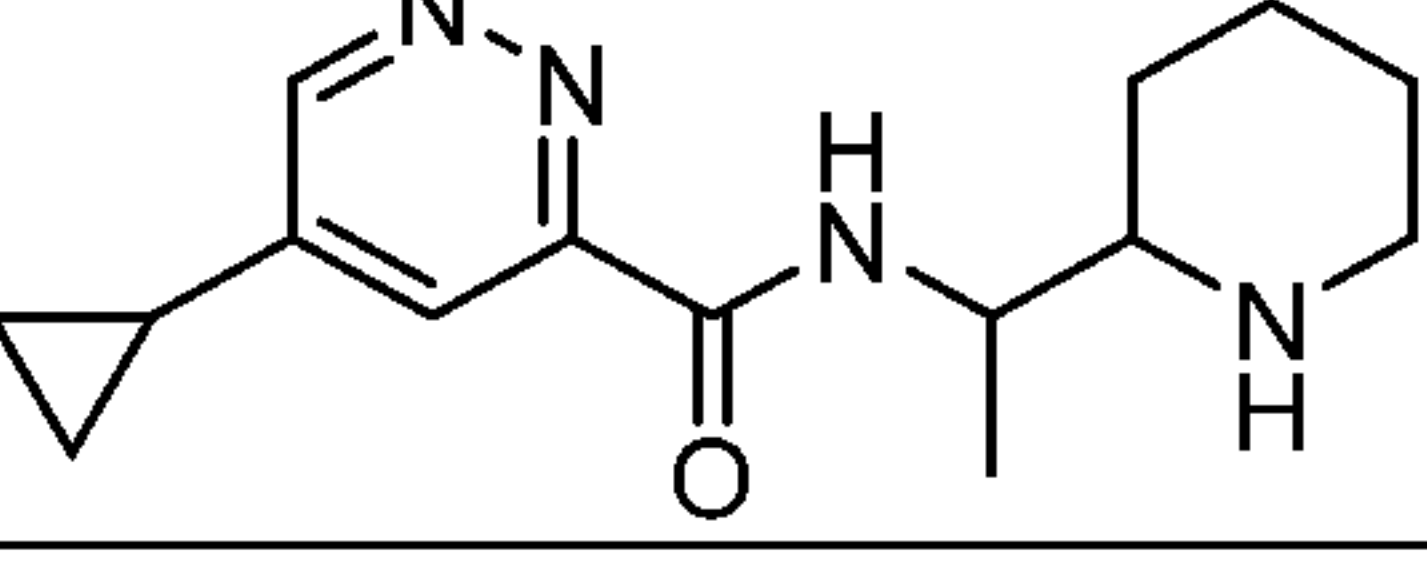
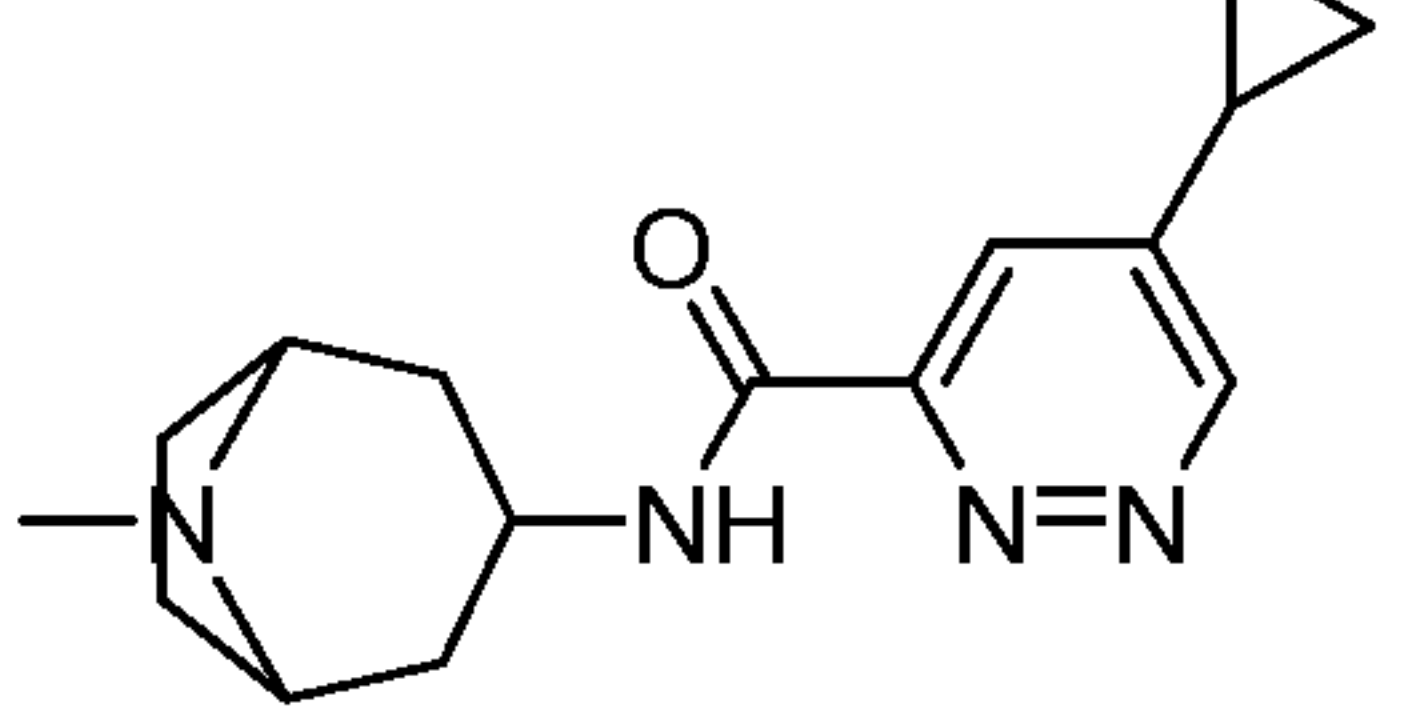
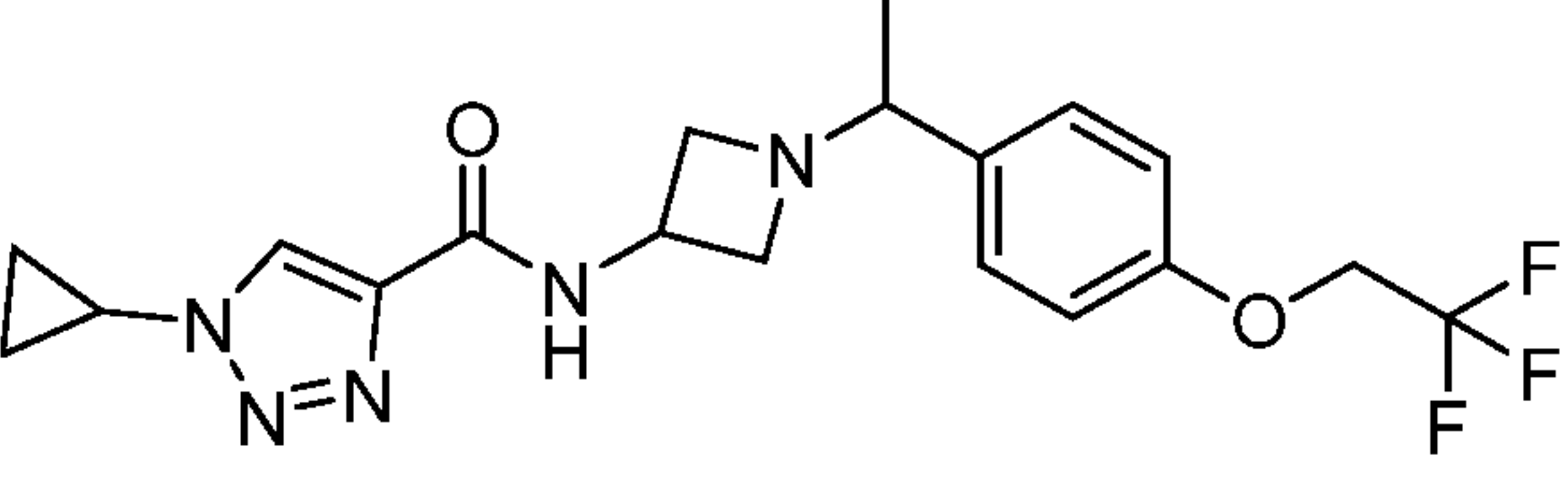
None	None	
		
917	918	
None	None	None
		
760	761	762

Table 5

Cpd. No.	Structure	Chemical Name
870		(R)-1-cyclopropyl-N-(1-(1-(2-methoxyphenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide
871		1-cyclopropyl-N-(1-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide
872		1-cyclopropyl-N-(1-(1-methylpiperidin-2-yl)ethyl)-1H-1,2,3-triazole-4-carboxamide
873		5-cyclopropyl-N-(1-(1-methylpiperidin-2-yl)ethyl)pyridazine-3-carboxamide
874		N-(1-(2-(4-(benzyloxy)phenyl)propan-2-yl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide
875		N-(1-(1-(4-(benzyloxy)phenyl)cyclopropyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide
876		1-cyclopropyl-N-(1-(4-(1-hydroxy-2-phenylethyl)benzyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide

877		1-cyclopropyl-N-(1-(4-(pyridin-3-ylmethoxy)benzyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide
878		N-(1-(4-((1,3,4-thiadiazol-2-yl)methoxy)benzyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide
879		1-cyclopropyl-N-(1-isopropylazetidin-3-yl)-1H-imidazole-4-carboxamide
880		1-cyclopropyl-N-(3-(dimethylamino)propyl)-1H-1,2,3-triazole-4-carboxamide
881		N-(1-(1-(4-(benzyloxy)-3-methoxyphenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide
882		N-(1-(1-(3-(2-chlorophenyl)-1H-indazol-5-yl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide
883		1-cyclopropyl-N-(1-(1-(5-methoxypyridin-2-yl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide
884		1-cyclopropyl-N-(1-(1-(2-methyl-2H-indazol-5-yl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide
885		5-cyclopropyl-N-(1-(1-(3-methoxyphenyl)ethyl)azetidin-3-yl)pyridazine-3-carboxamide

886		N-(1-(1-(5-chloro-2-(difluoromethoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide
887		1-cyclopropyl-N-(1-(1-(4-(benzyloxy)phenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide
888		N-(1-(1-(3-(2-aminoethoxy)-2-chlorophenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide
889		N-(1-(1-(2-chloro-3-(2-(methylamino)ethoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide
890		N-(1-(1-(2-chloro-3-(2-(dimethylamino)ethoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide
891		N-(1-(1-(2-chloro-3-(2-(2-hydroxypropoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide
892		N-(1-(1-(2-chloro-3-(2-(2-hydroxy-2-methylpropoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide
893		N-(1-(1-(2-chloro-3-(2,3-dihydroxypropoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide
894		N-(1-(1-(2-chloro-5-methoxyphenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide

895		N-(1-(1-(5-chloro-2-(trifluoromethyl)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide
896		1-cyclopropyl-N-(1-(1-(4-((4-methylbenzyl)oxy)phenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide
897		N-(1-(bicyclo[2.2.2]octan-1-ylmethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide
898		1-cyclopropyl-N-(1-((4-methoxybicyclo[2.2.2]octan-1-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide
899		1-cyclopropyl-N-(2,2-dimethyl-1-(1-phenylethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide
900		1-cyclopropyl-N-(1-(piperidin-2-yl)ethyl)-1H-1,2,3-triazole-4-carboxamide
901		5-cyclopropyl-N-(1-(piperidin-2-yl)ethyl)pyridazine-3-carboxamide
902		5-cyclopropyl-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)pyridazine-3-carboxamide
903		1-cyclopropyl-N-(1-(1-(4-(2,2,2-trifluoroethoxy)phenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide

904		1-cyclopropyl-N-(1-(1-(4-(piperidin-4-ylmethoxy)phenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide
905		1-cyclopropyl-N-(1-(1-(6-oxo-1,6-dihydropyridin-3-yl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide
906		N-(1-(1-(5-chloro-2-(4-fluorophenoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide
907		N-(1-(1-(4-((4-acetamidobenzyl)oxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide
908		1-cyclopropyl-N-(1-(1-(4-((phenylamino)methyl)phenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide
909		1-cyclopropyl-N-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide
910		N-(1-(1-(4-chlorophenyl)-2,2,2-trifluoroethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide

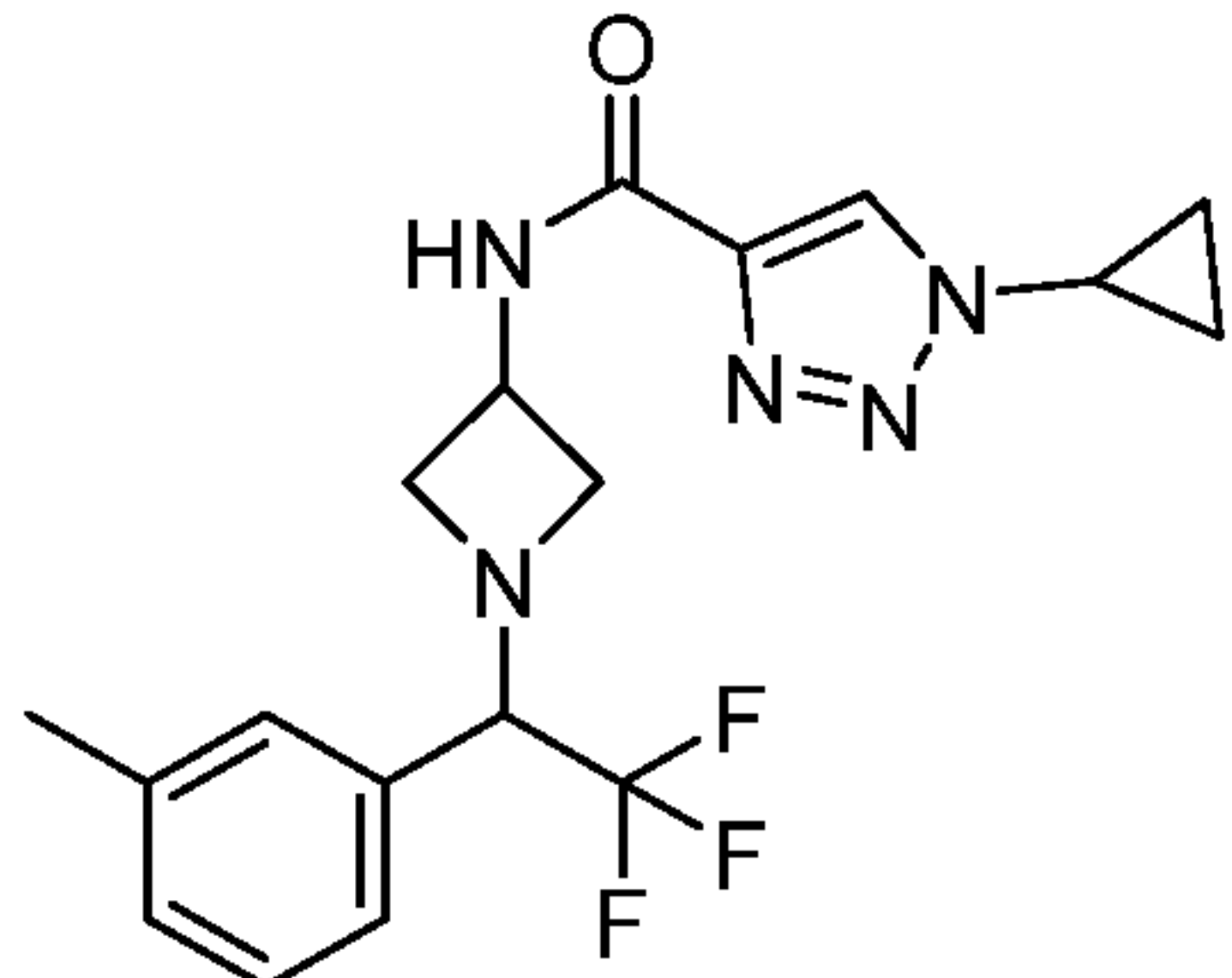
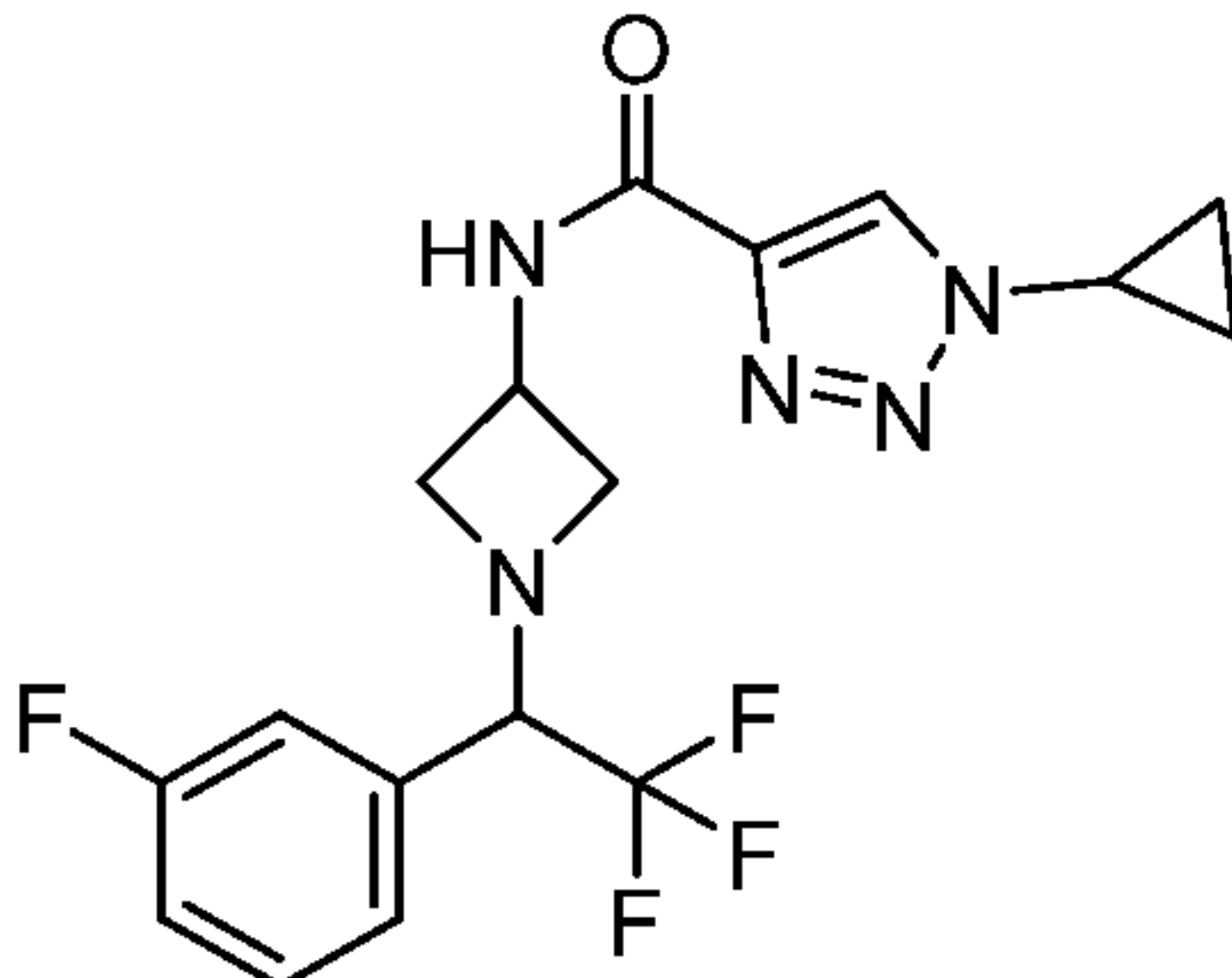
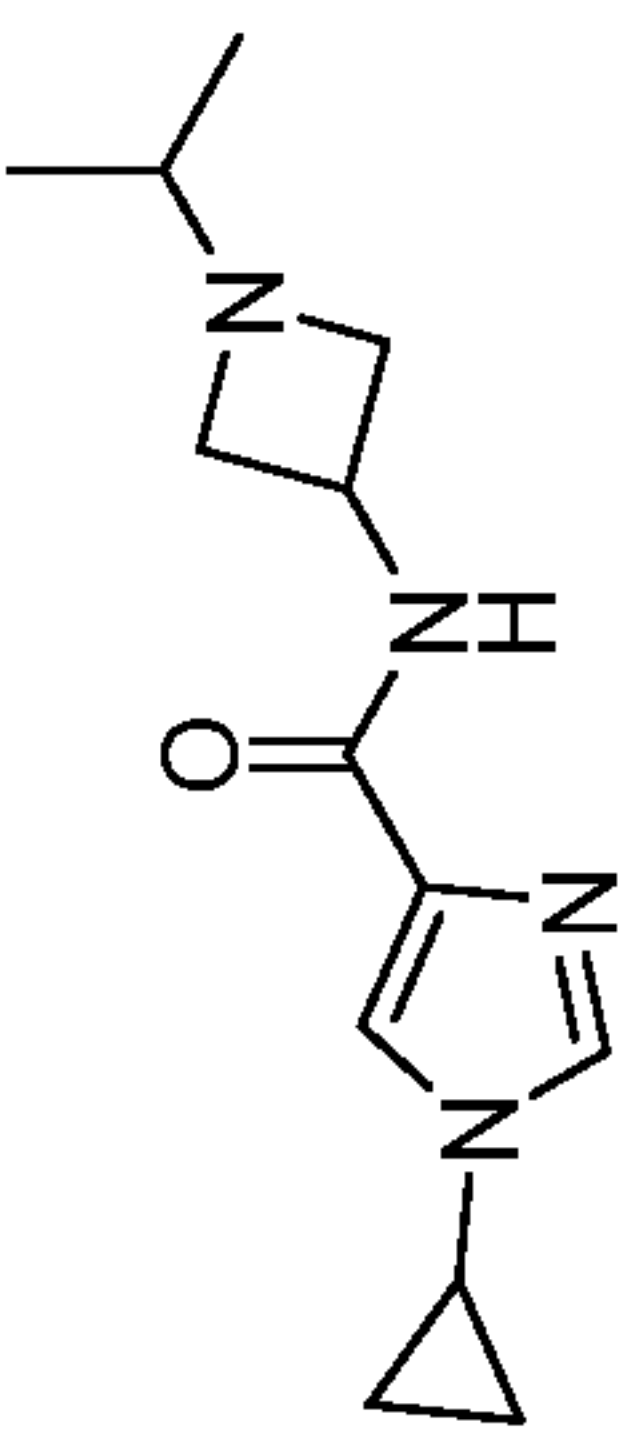
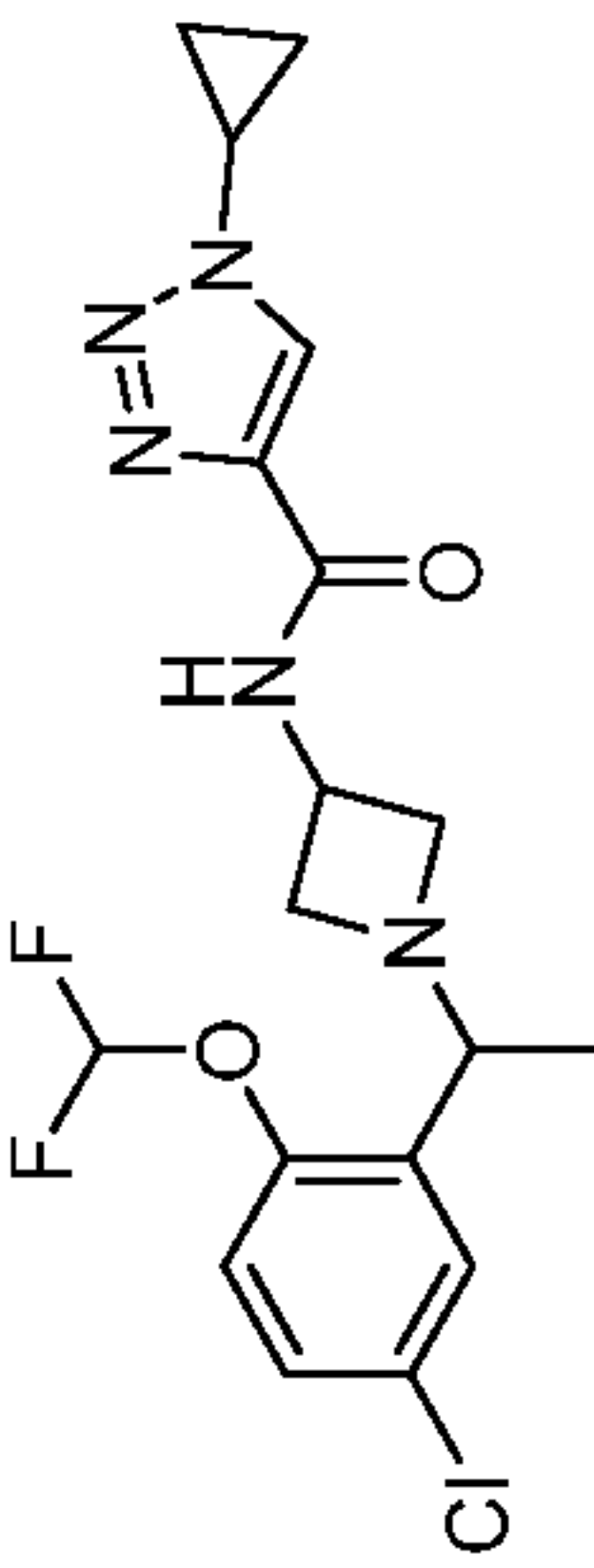
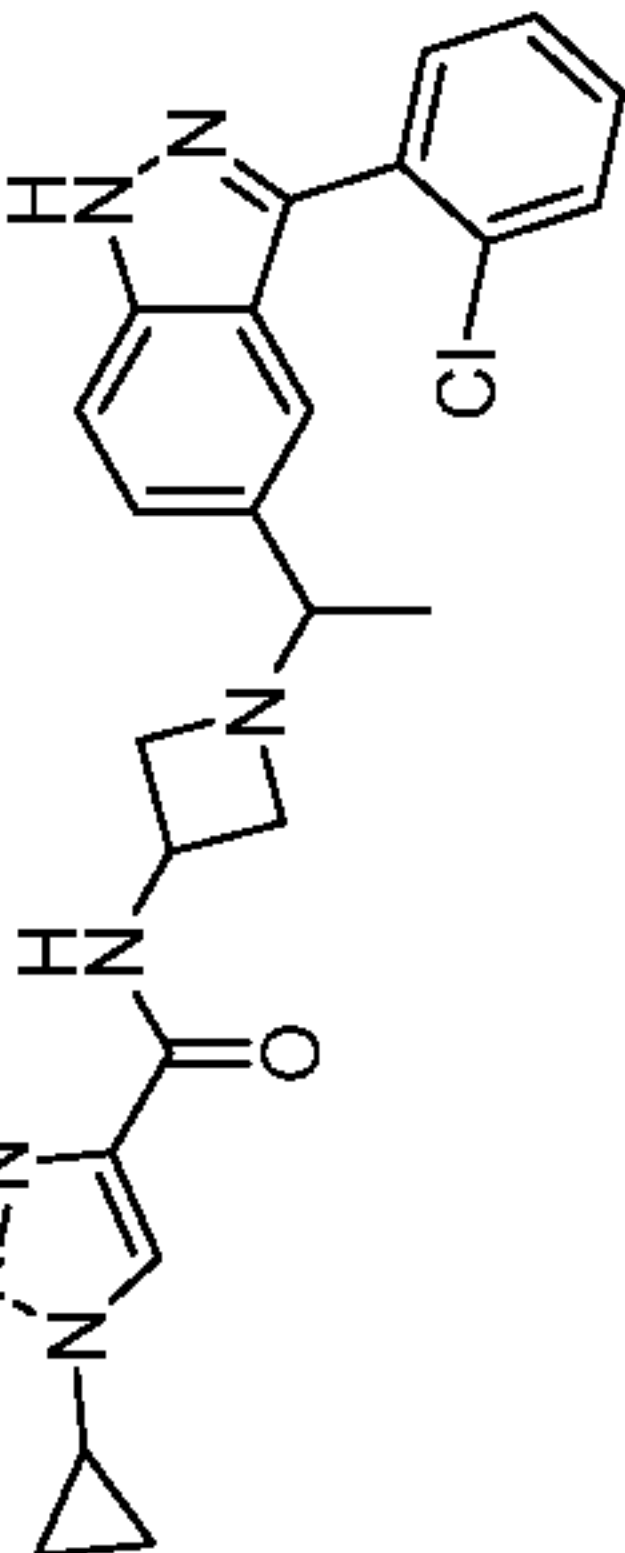
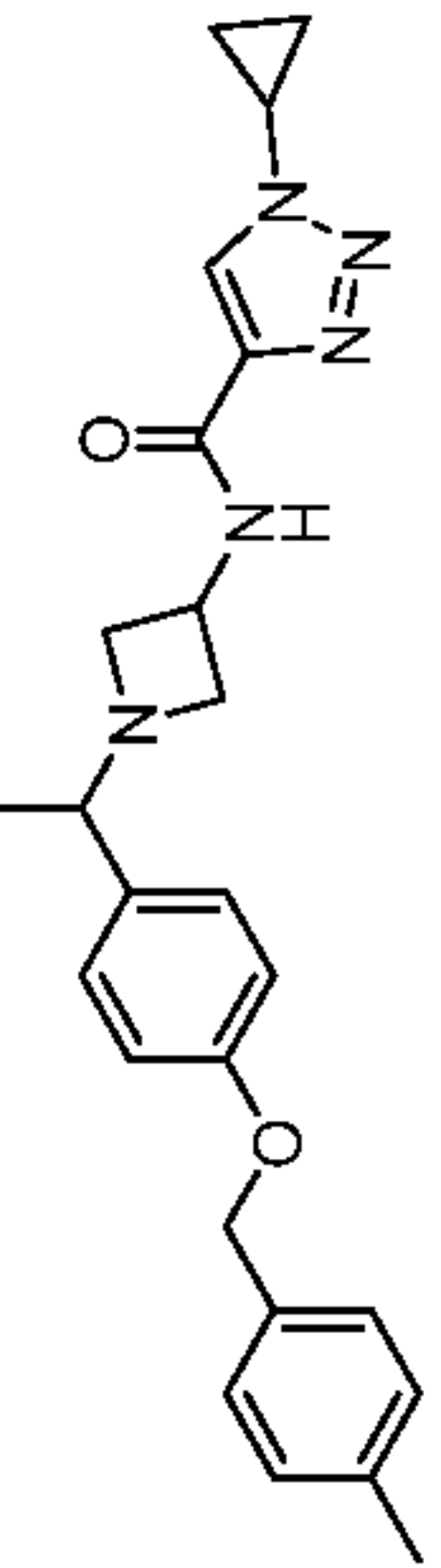
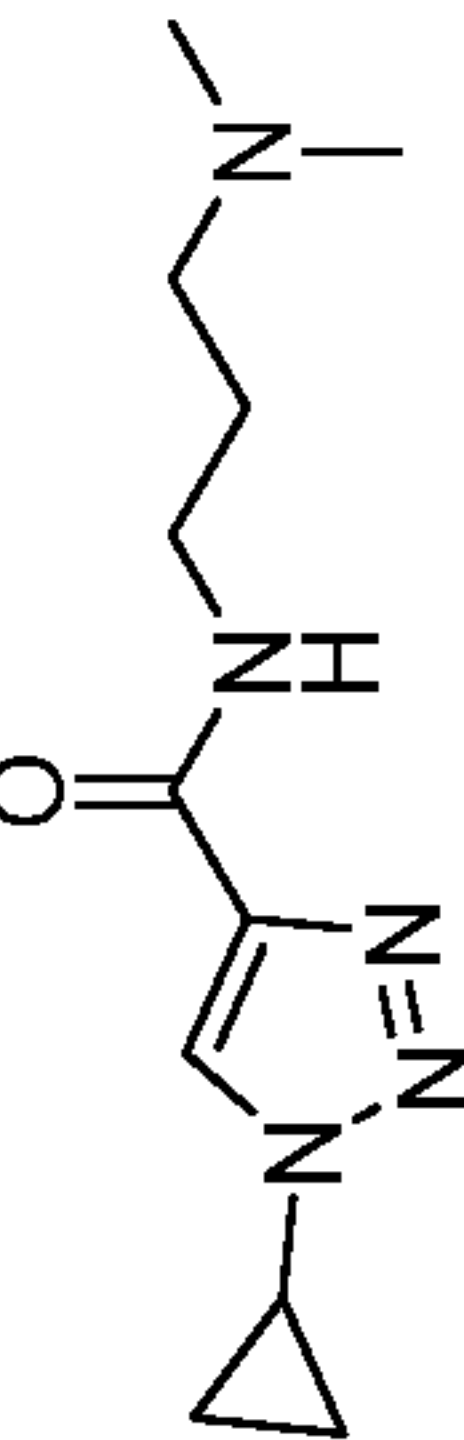
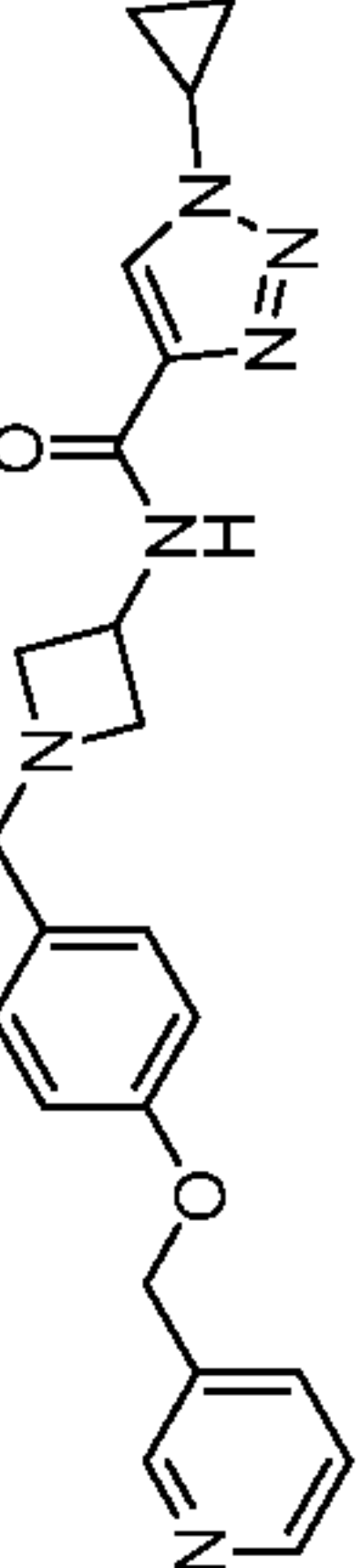
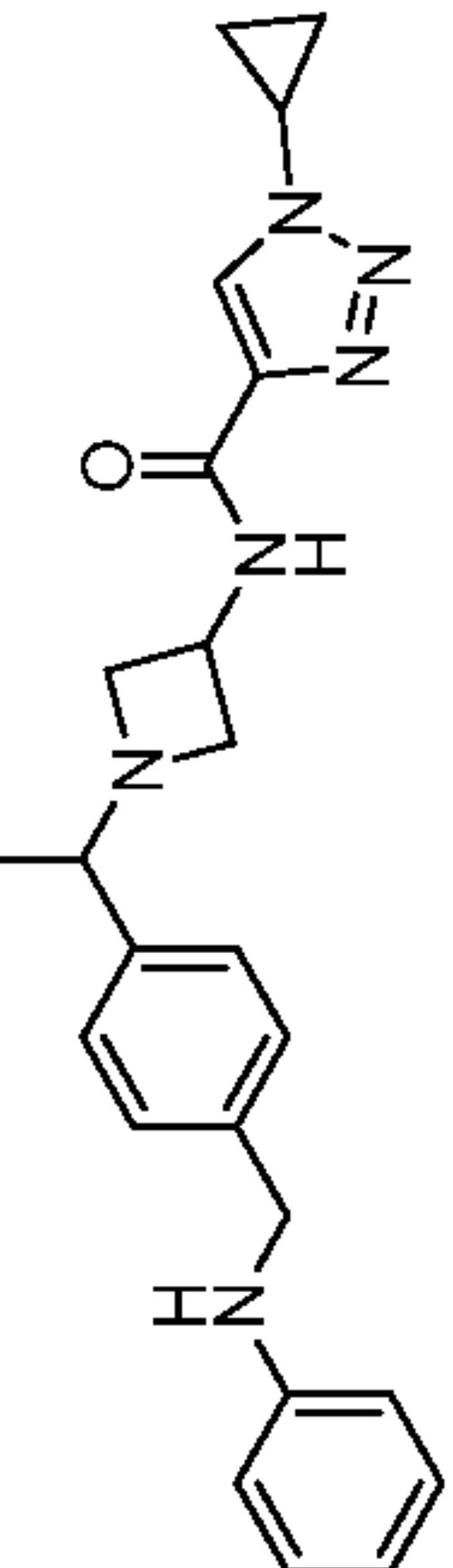
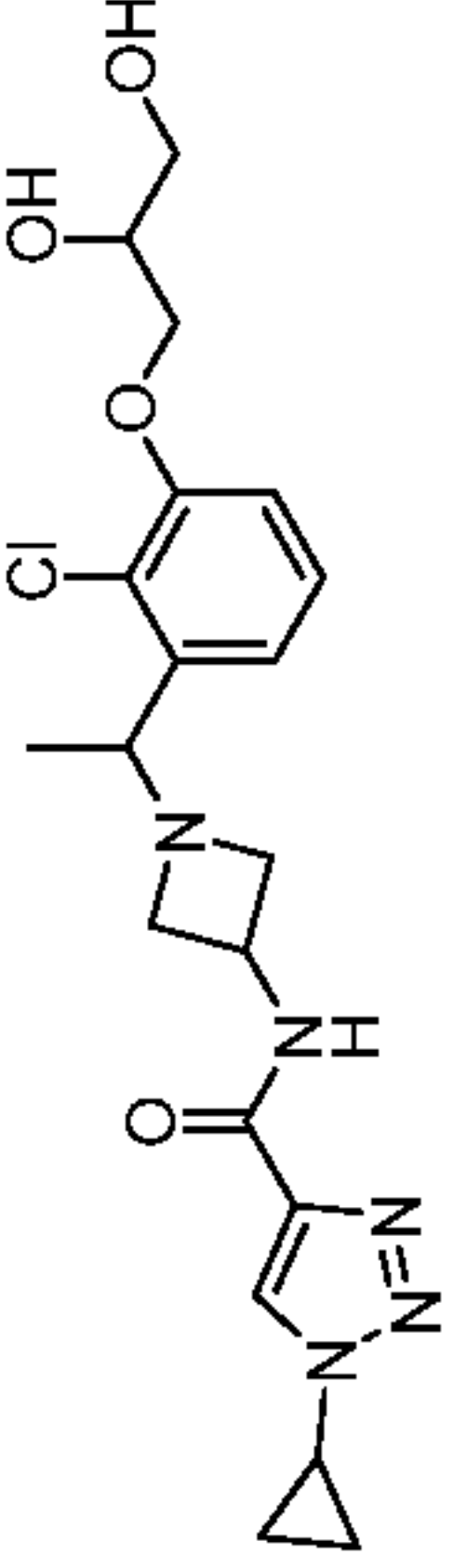
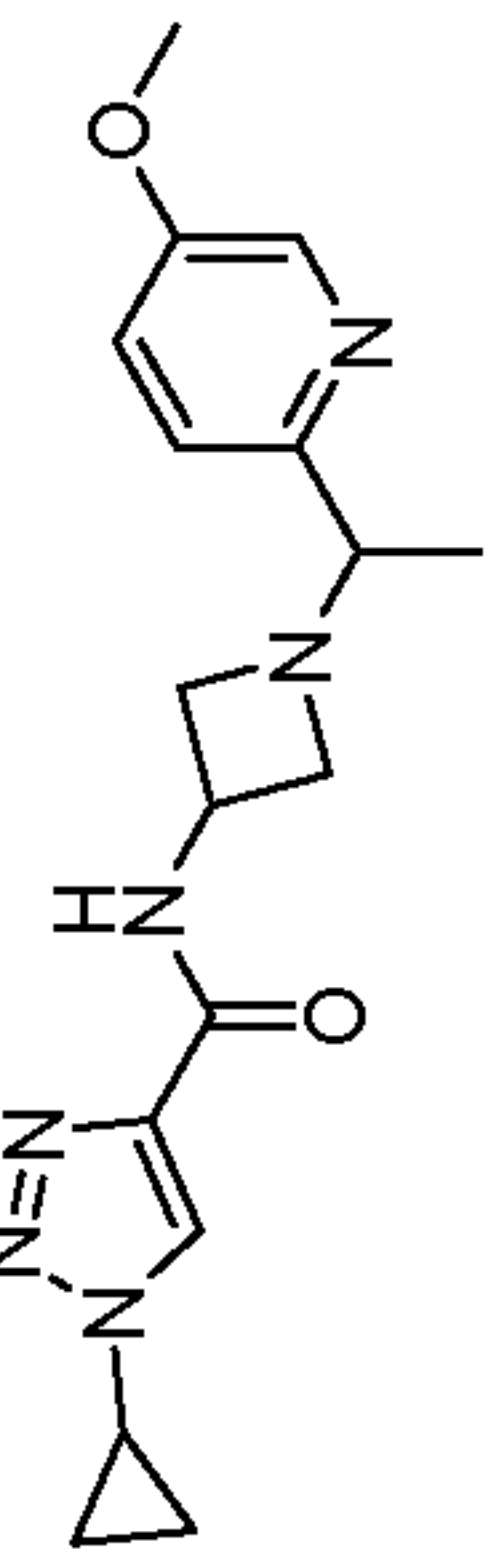
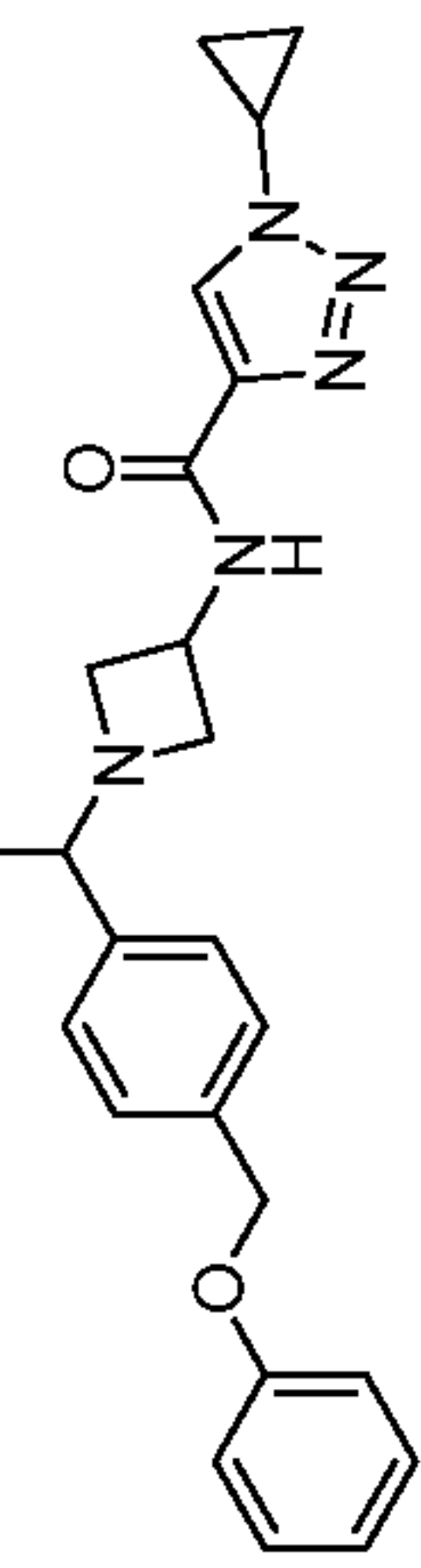
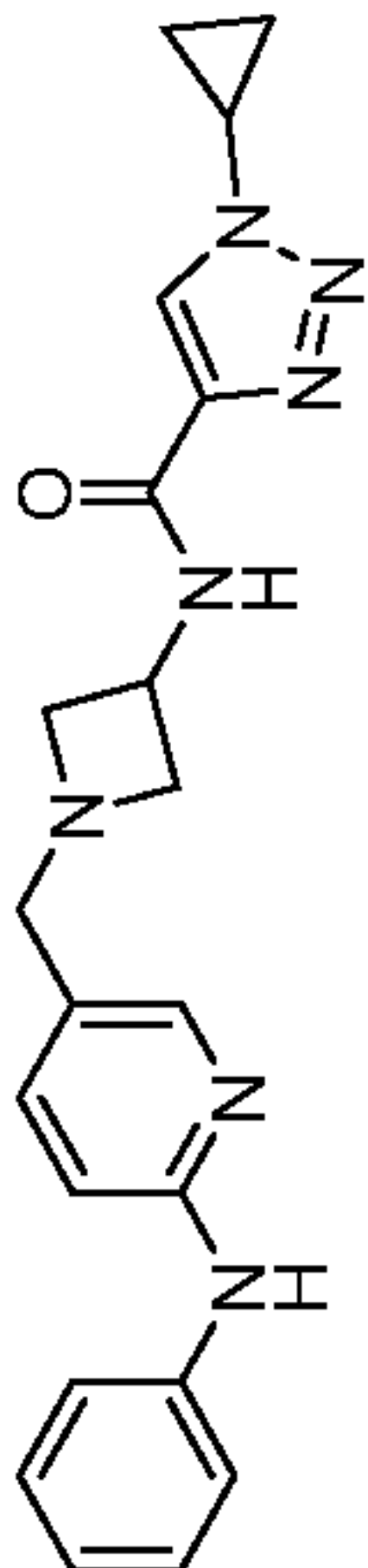
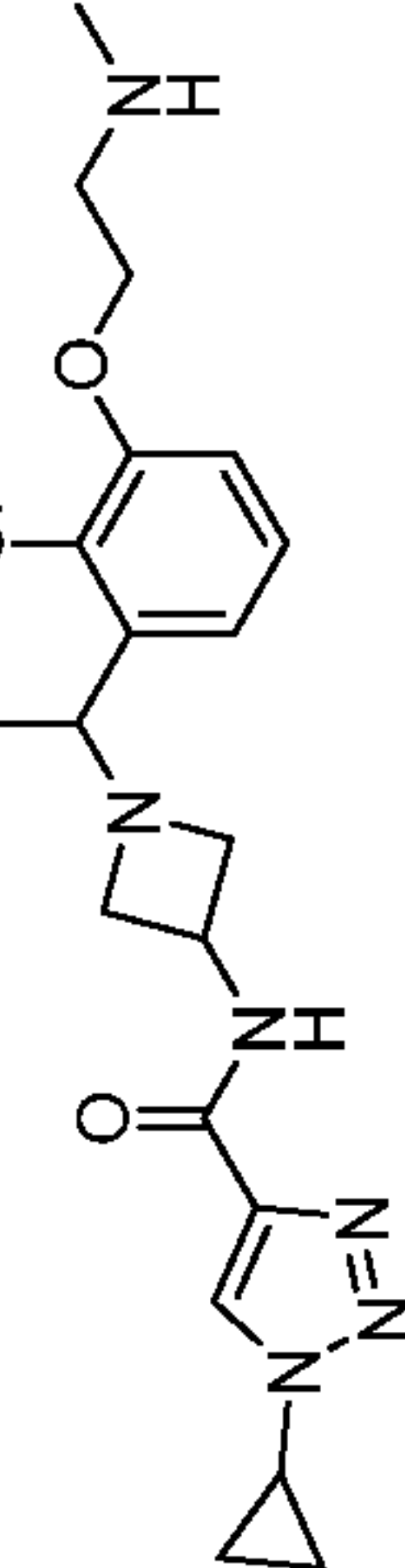
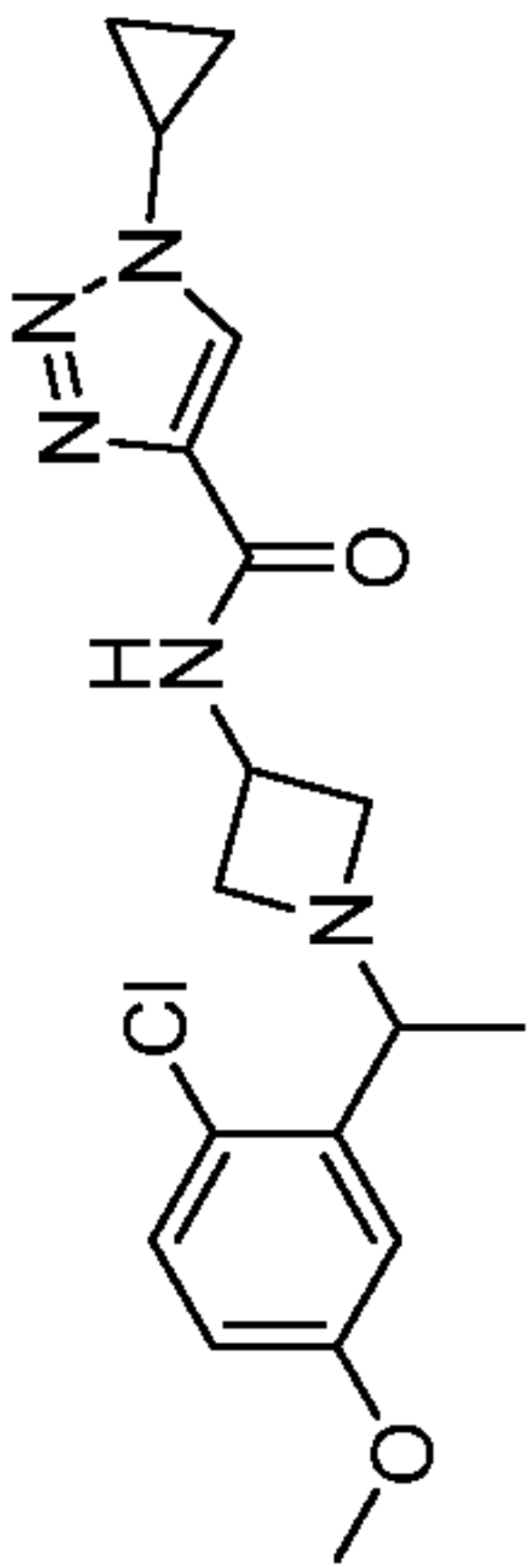
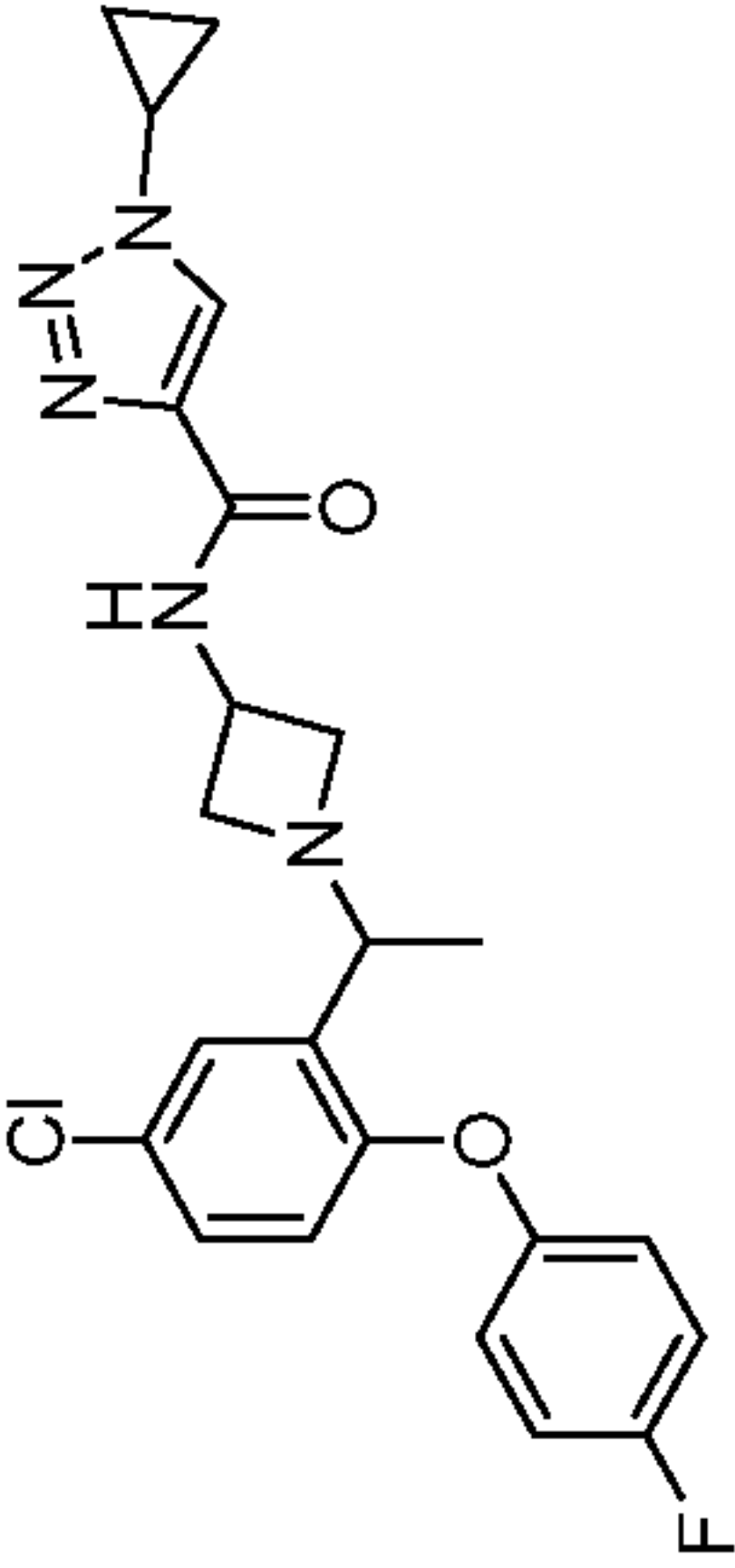
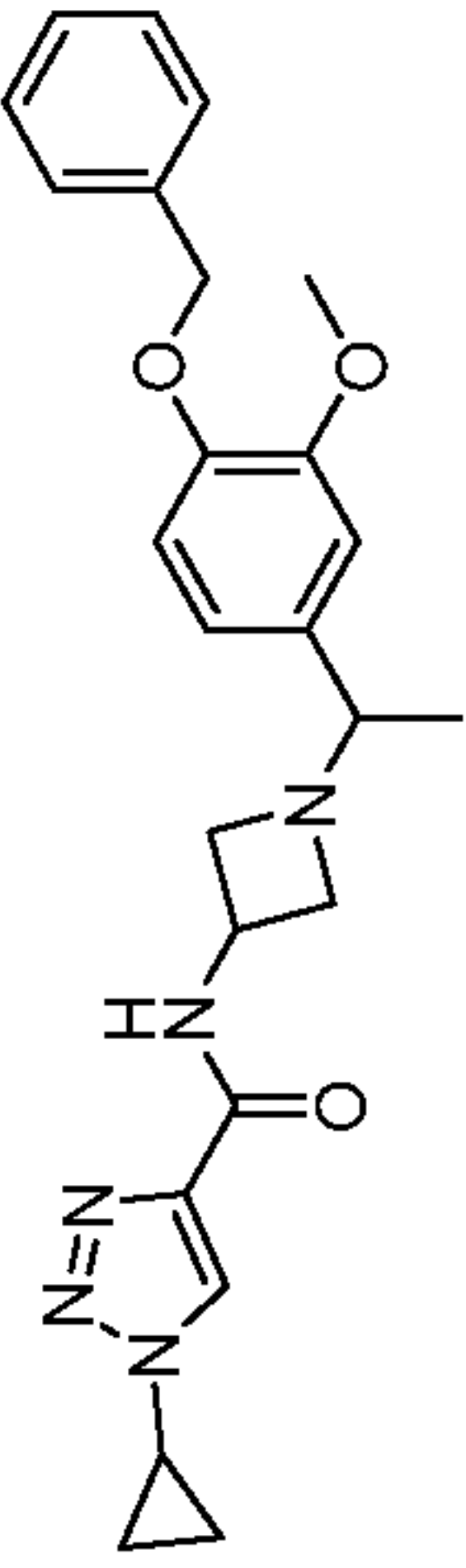
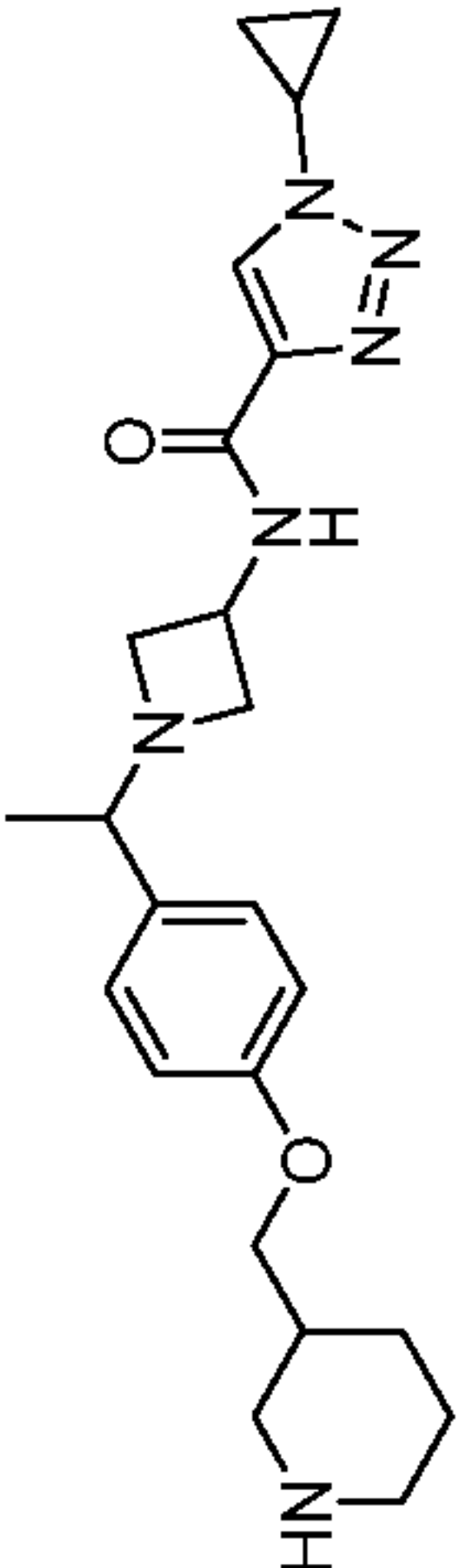
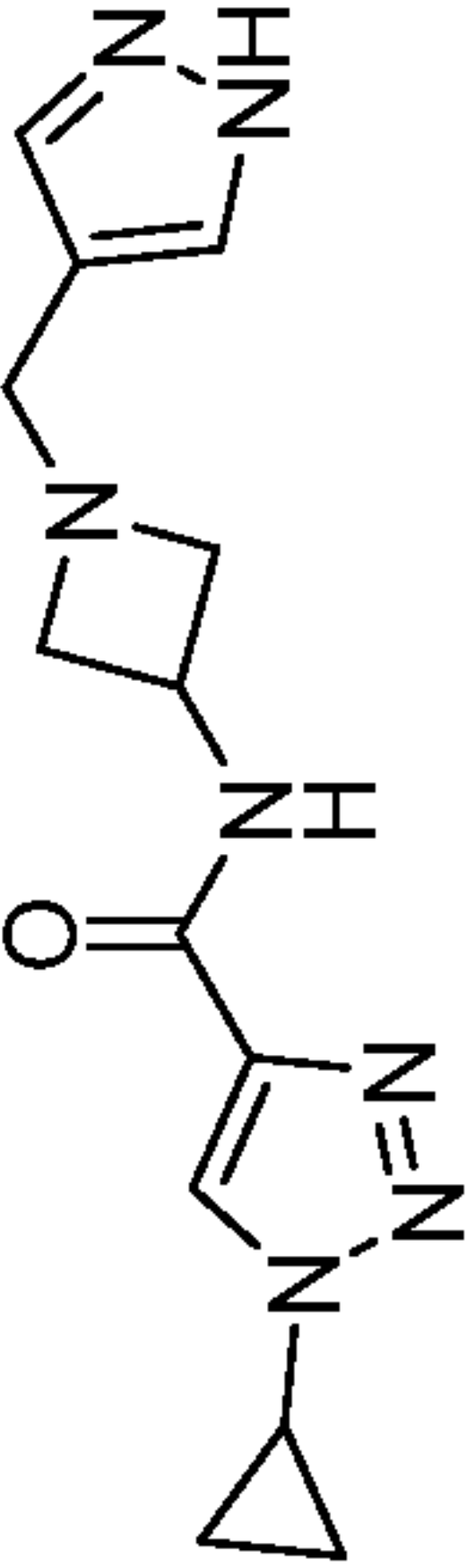
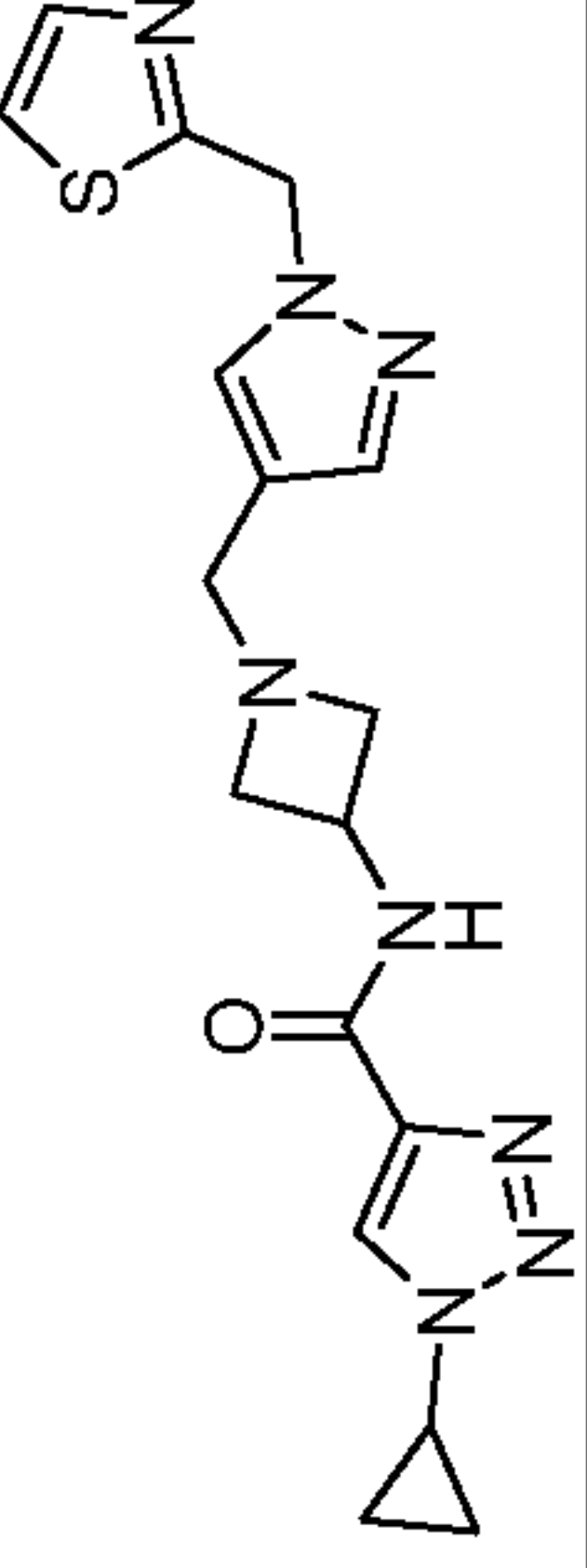
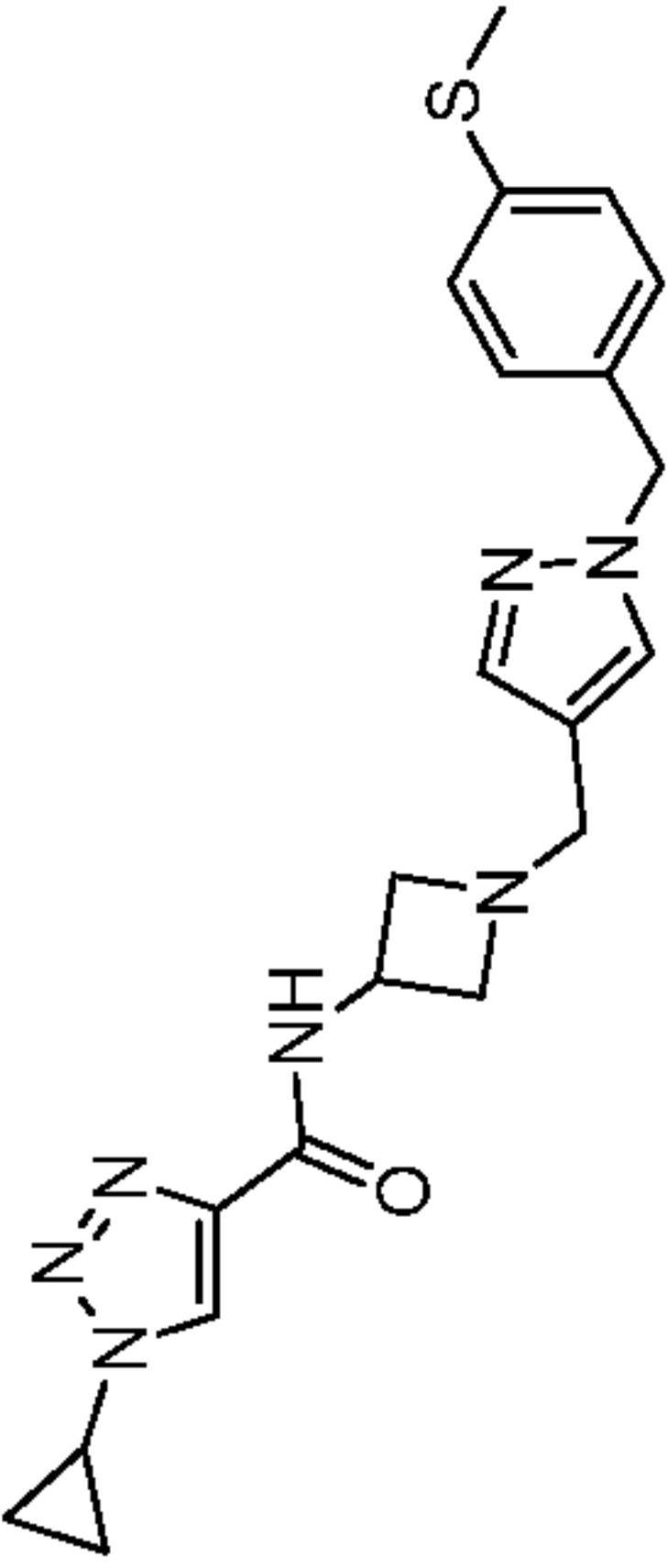
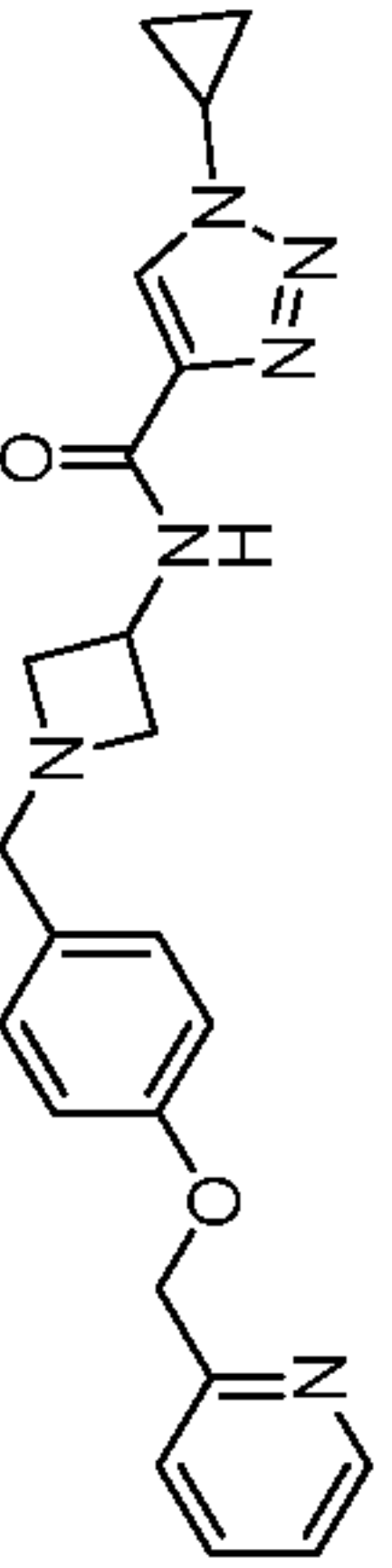
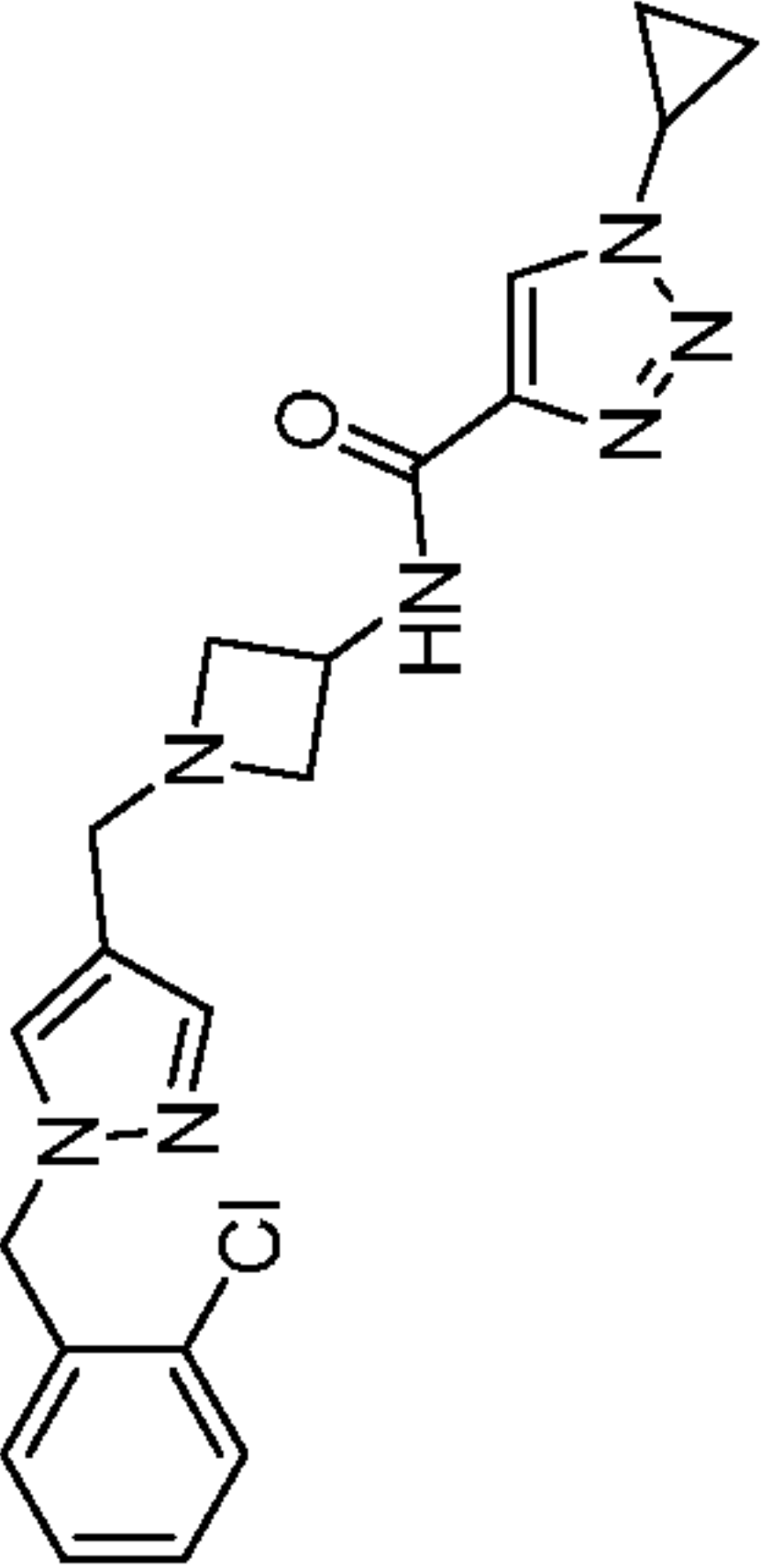
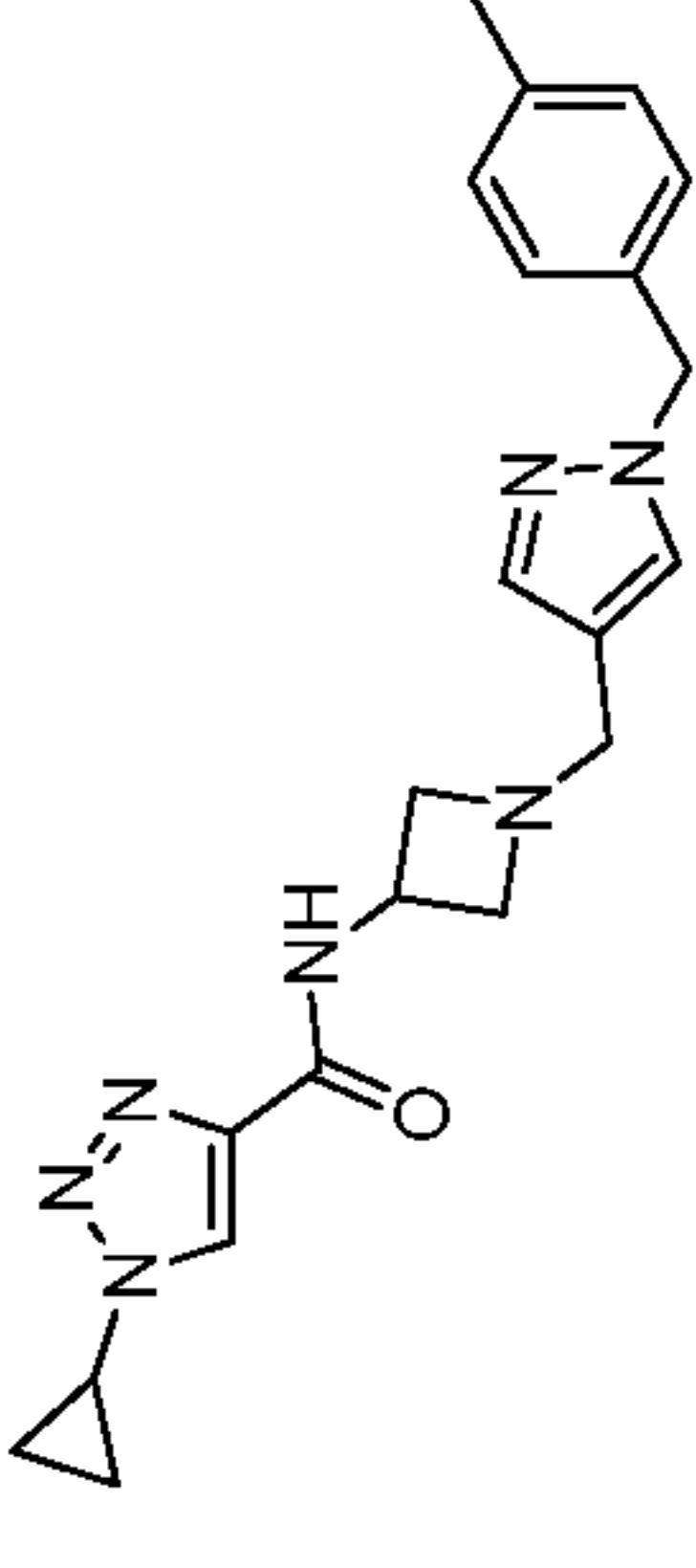
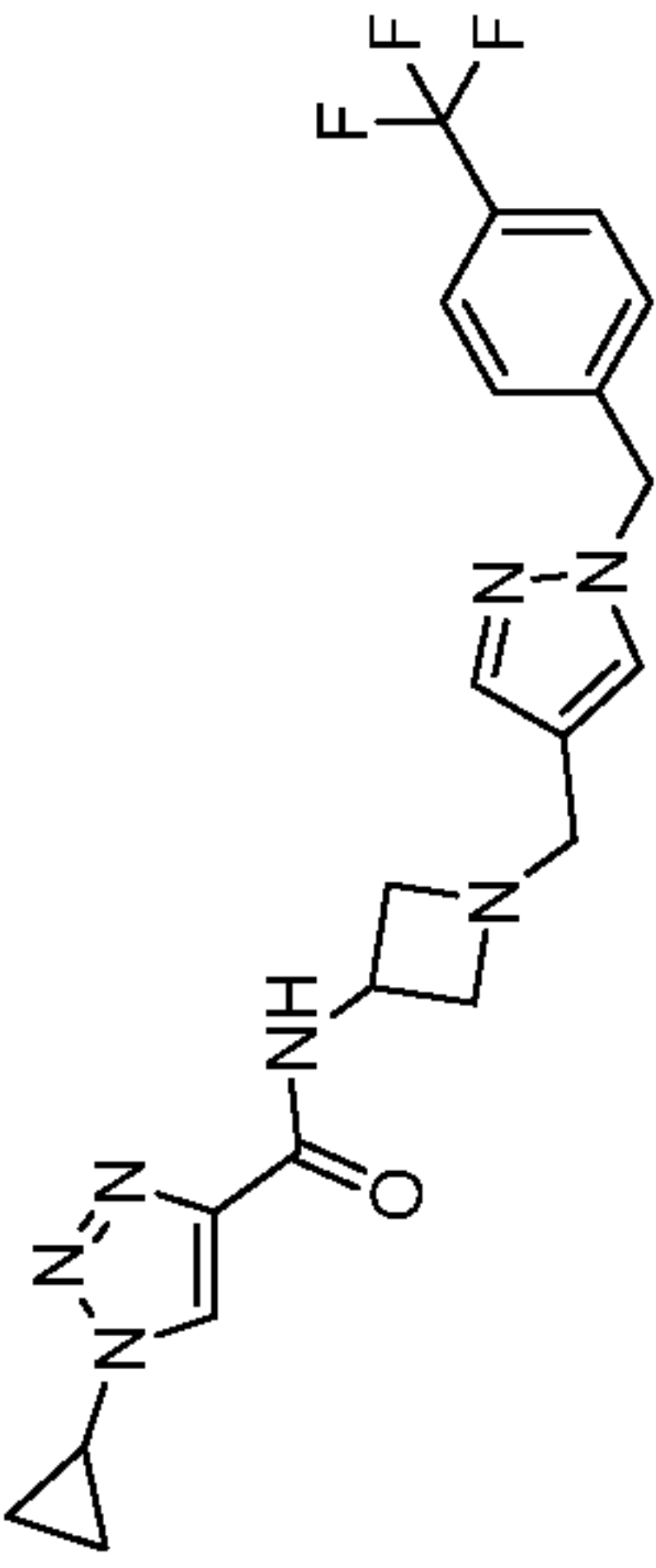
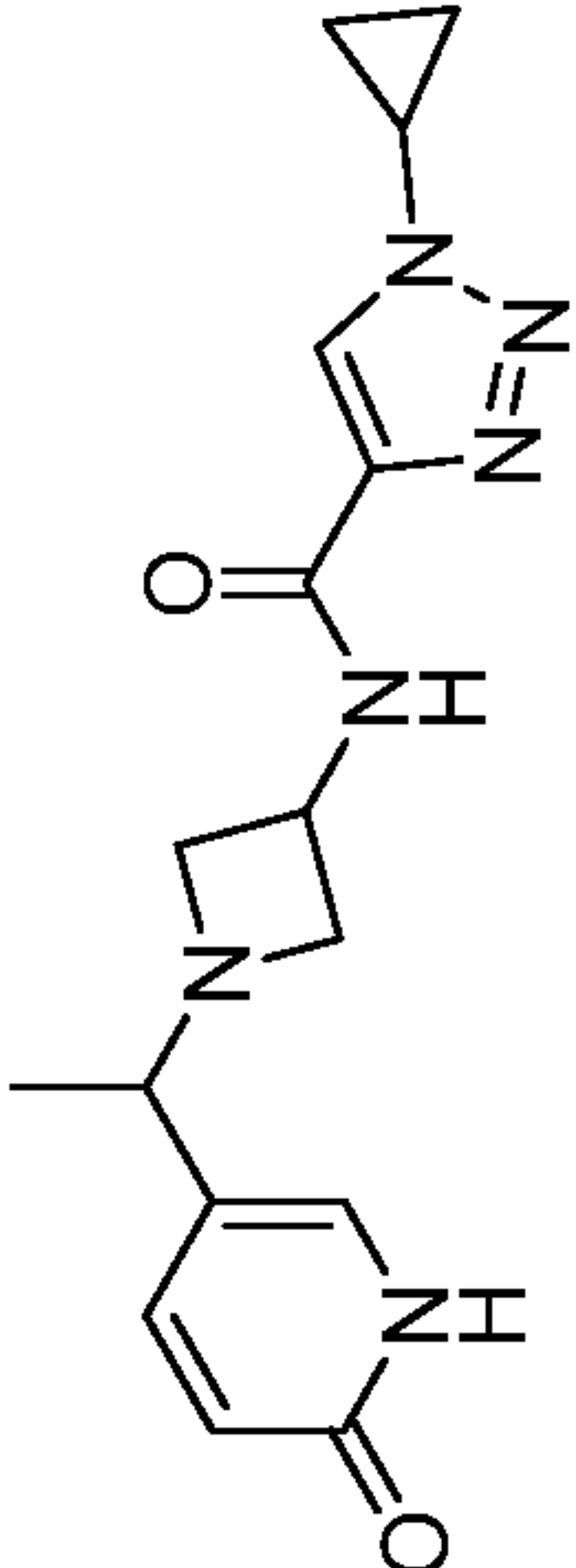
911		1-cyclopropyl-N-(1-(2,2,2-trifluoro-1-(m-tolyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide
912		1-cyclopropyl-N-(1-(2,2,2-trifluoro-1-(3-fluorophenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide

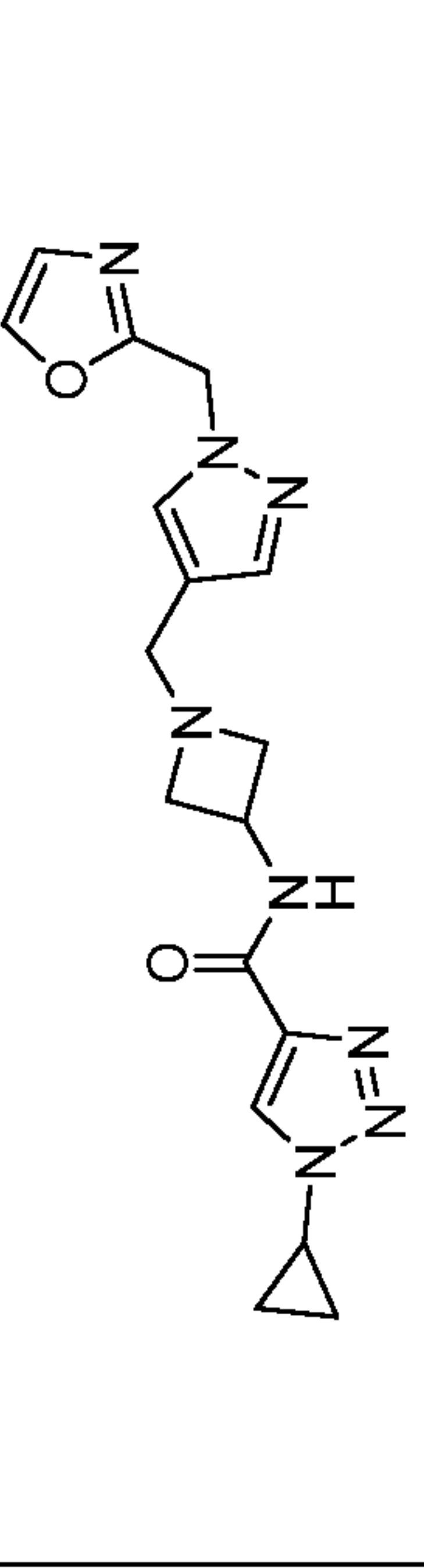
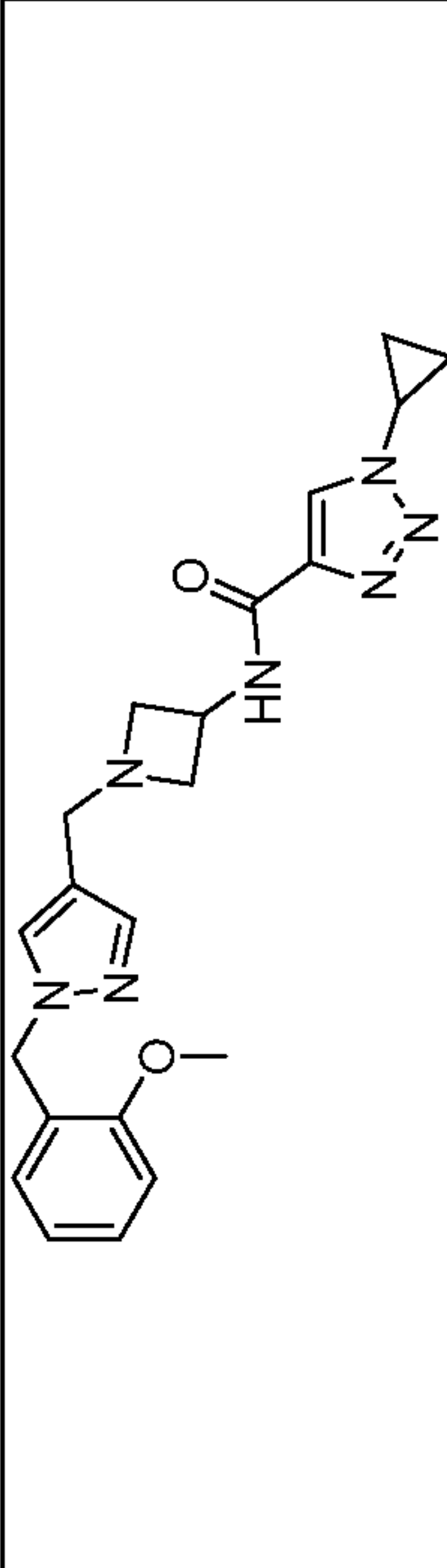
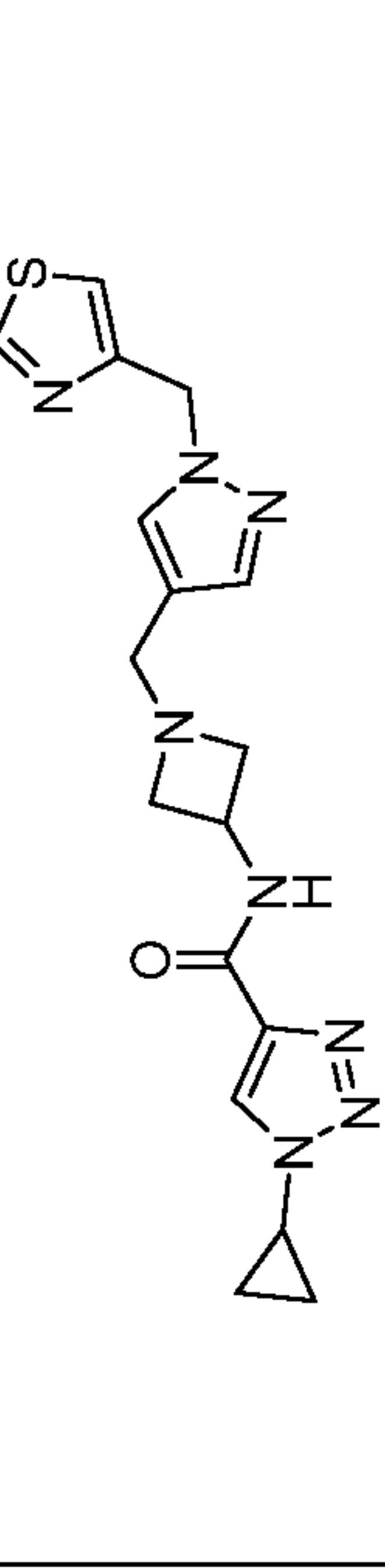
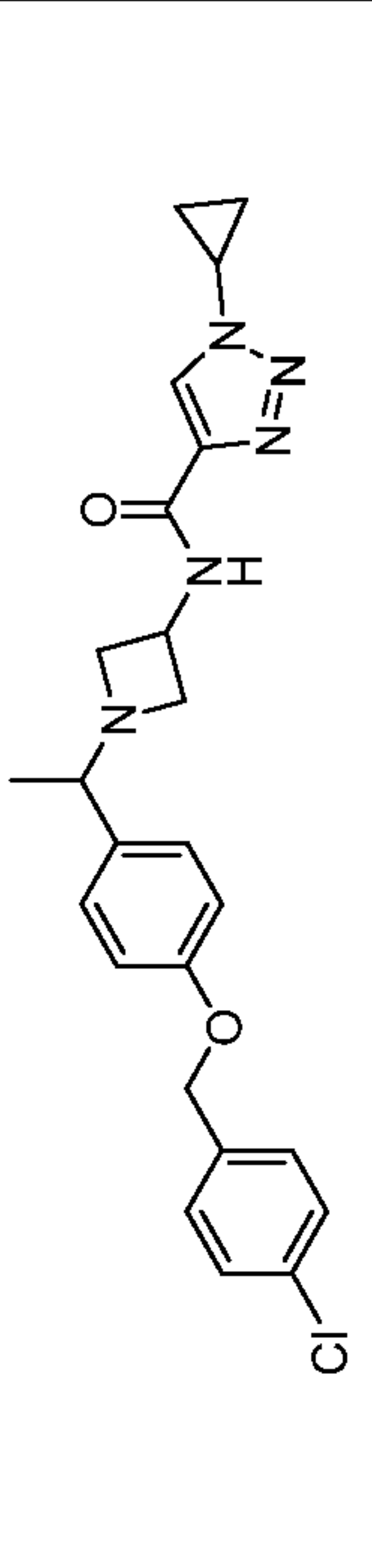
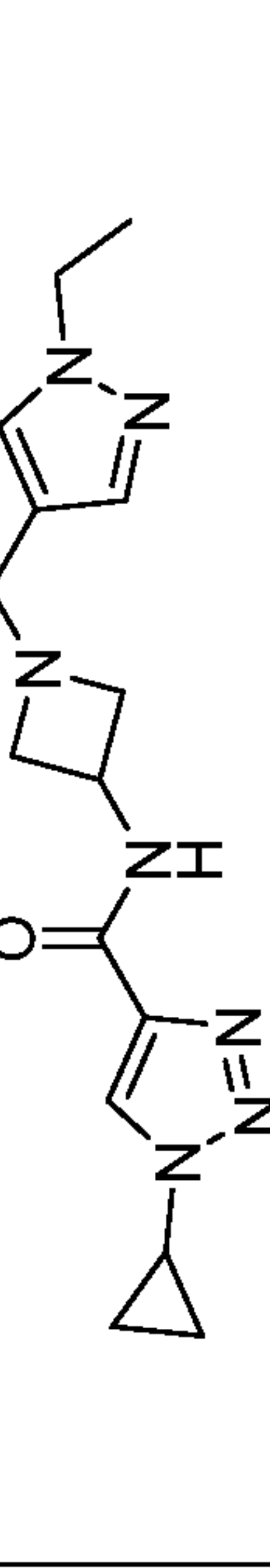
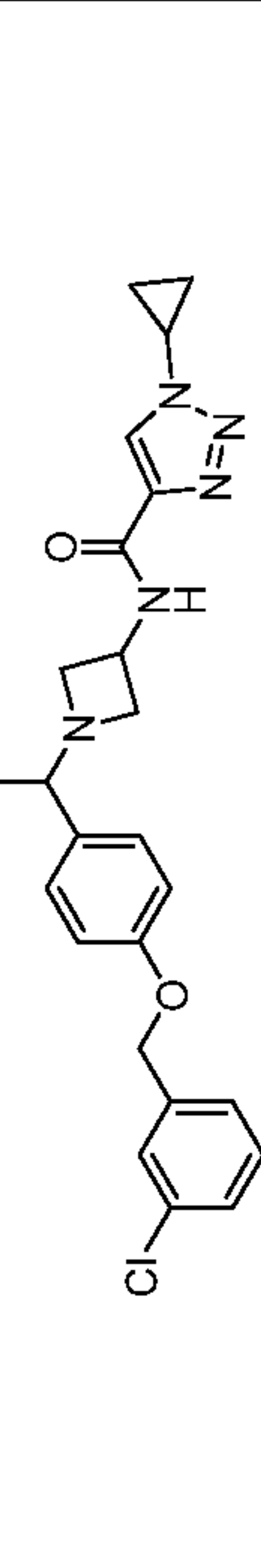
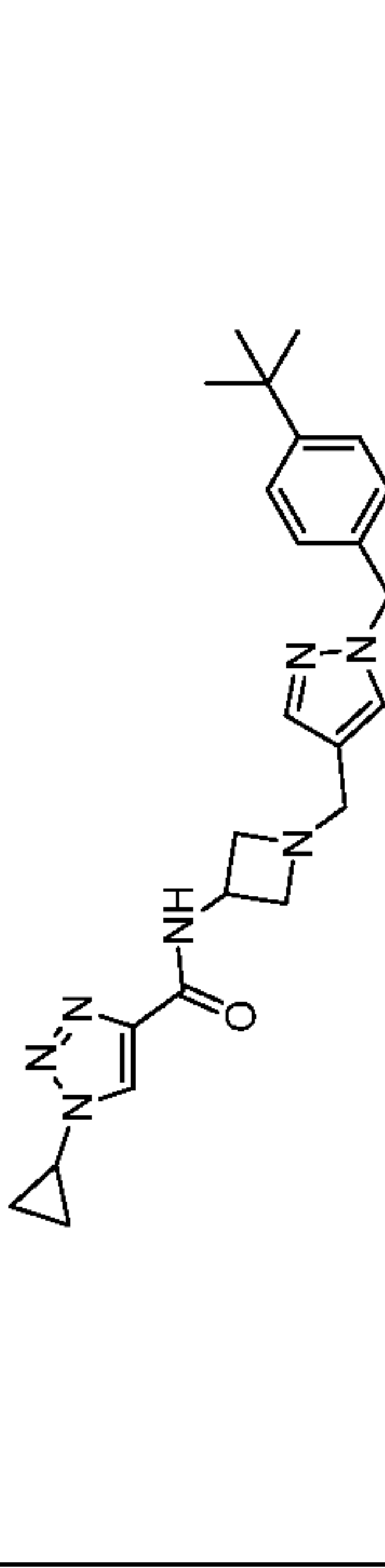
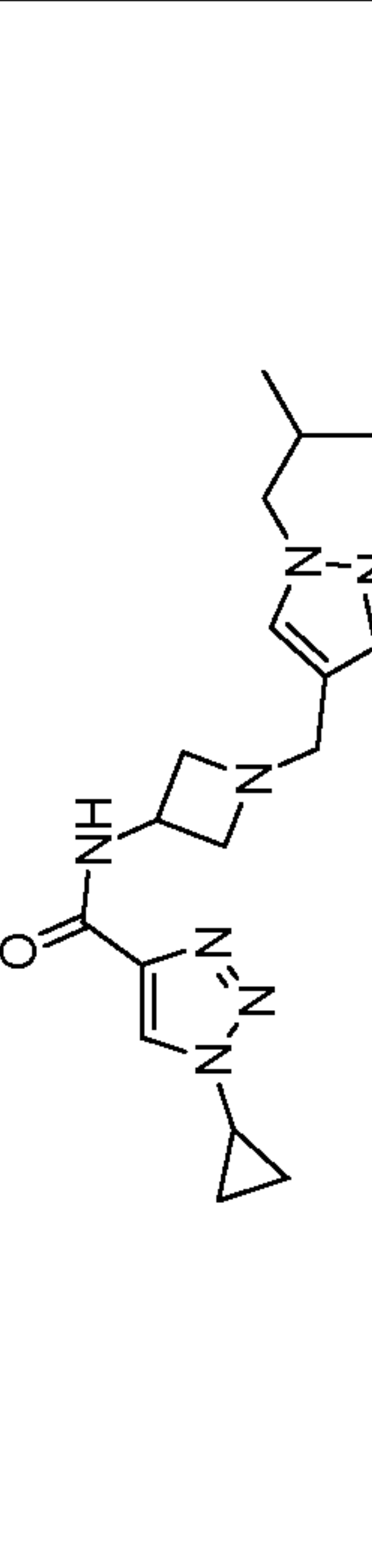
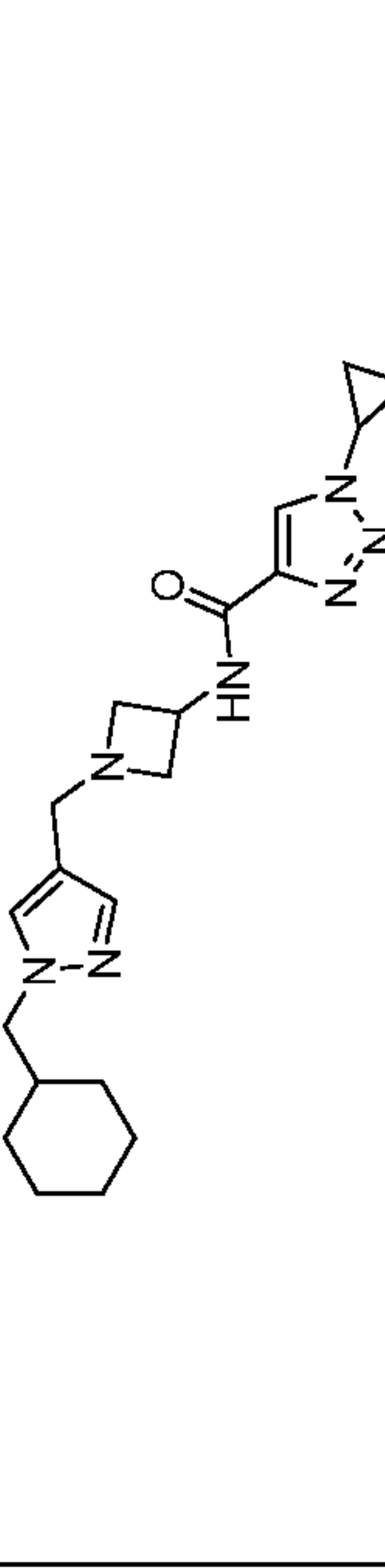
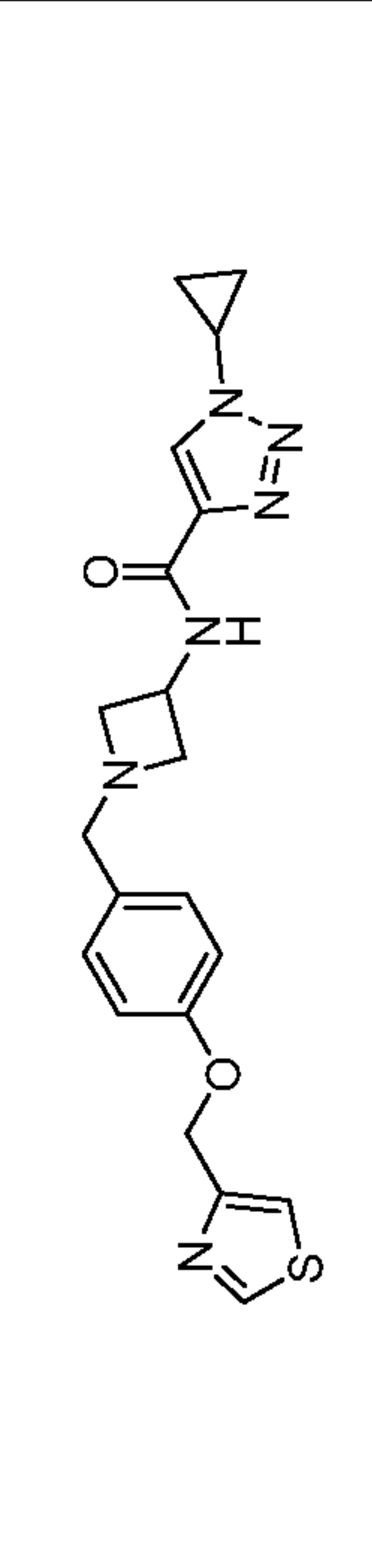
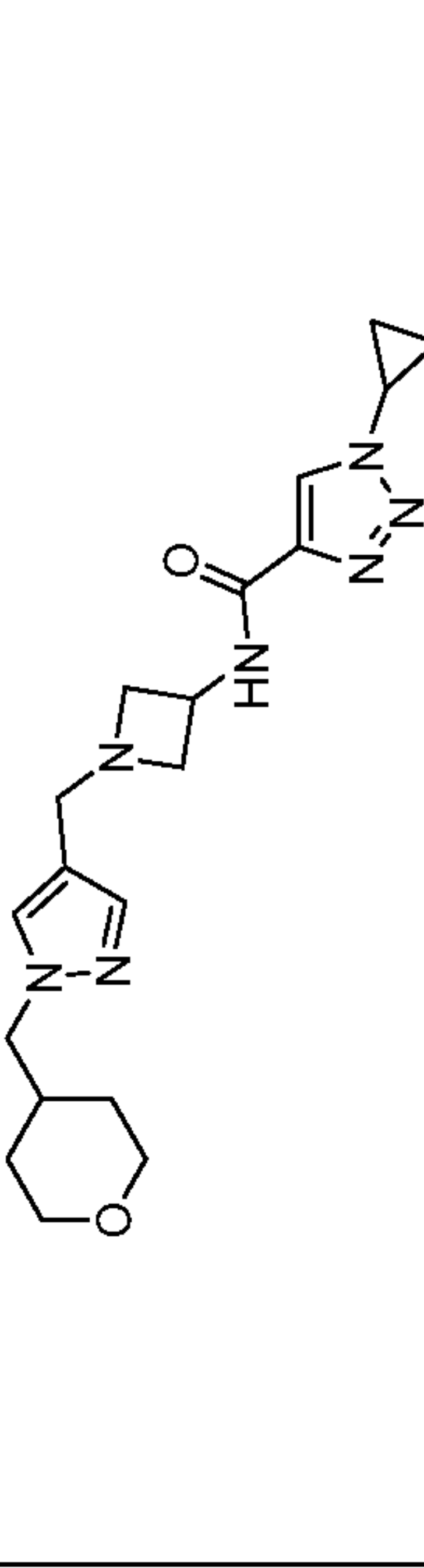
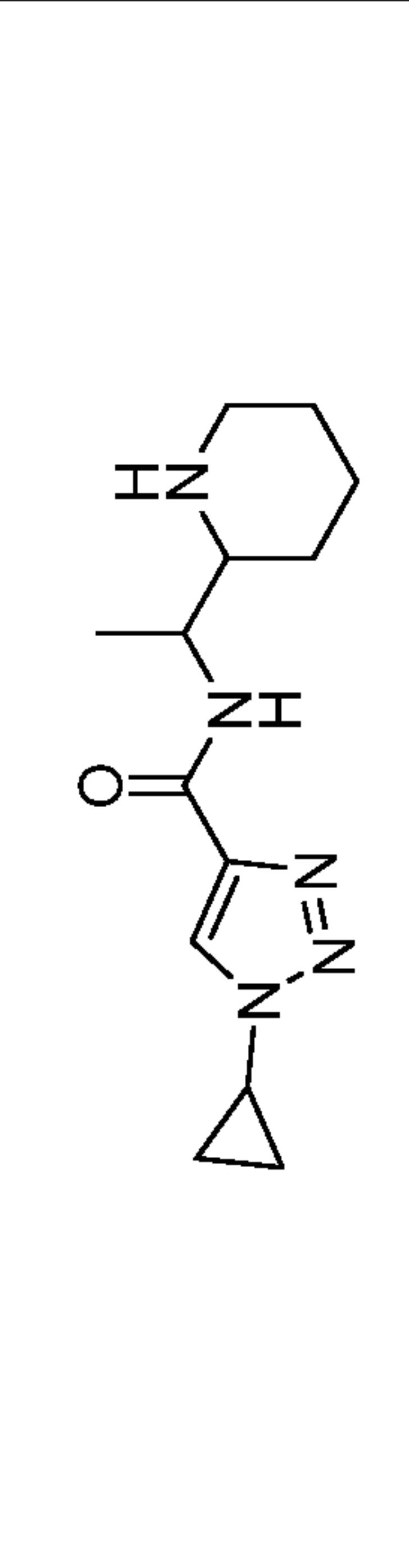
Table 6

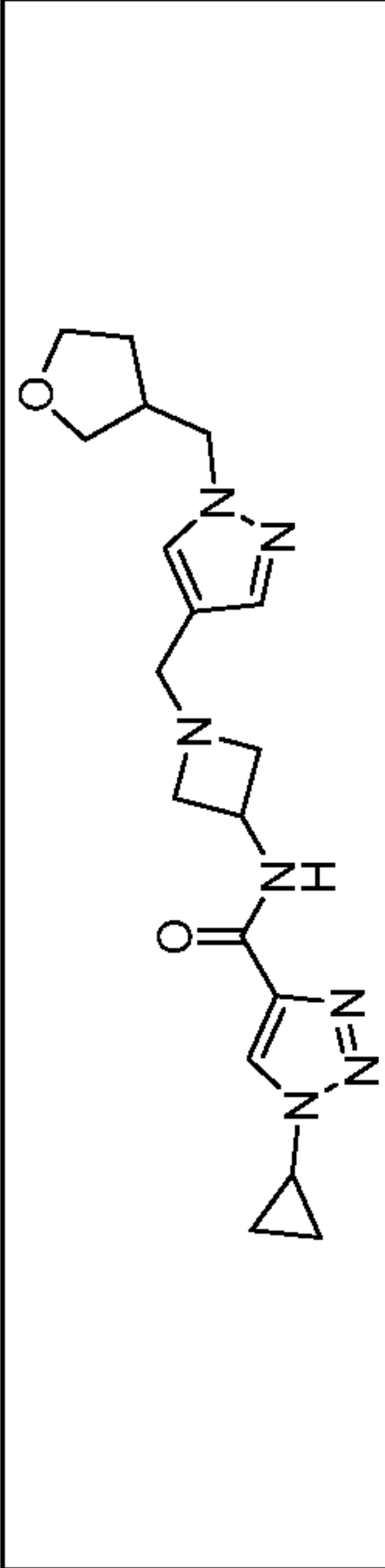
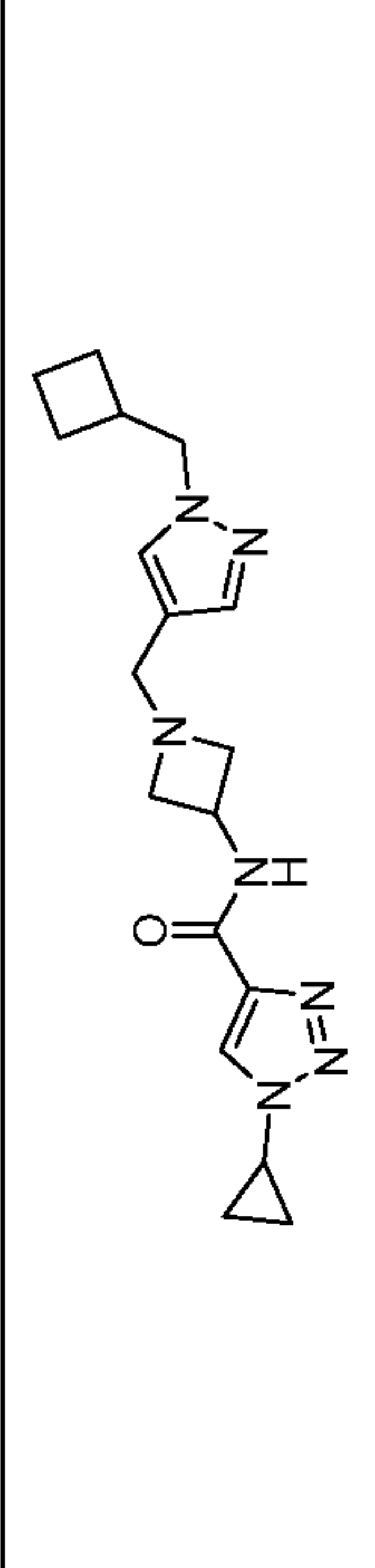
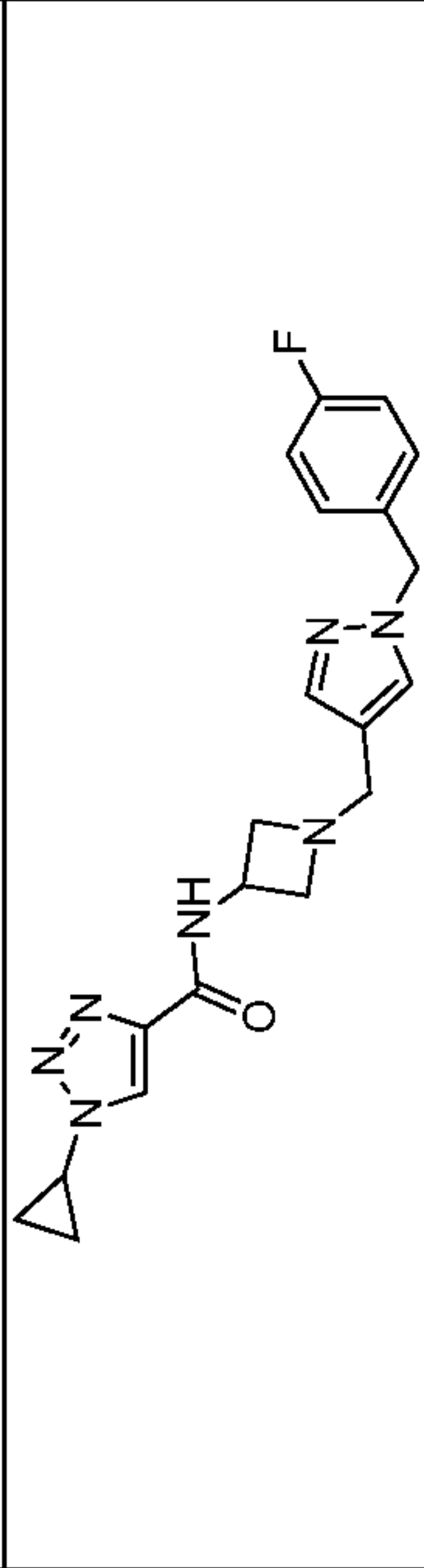
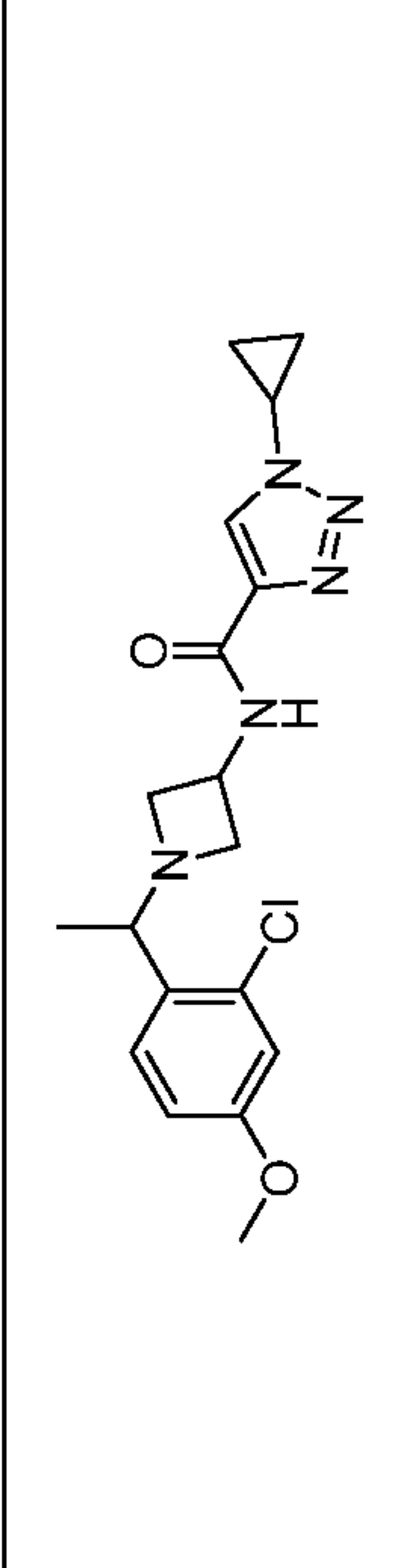
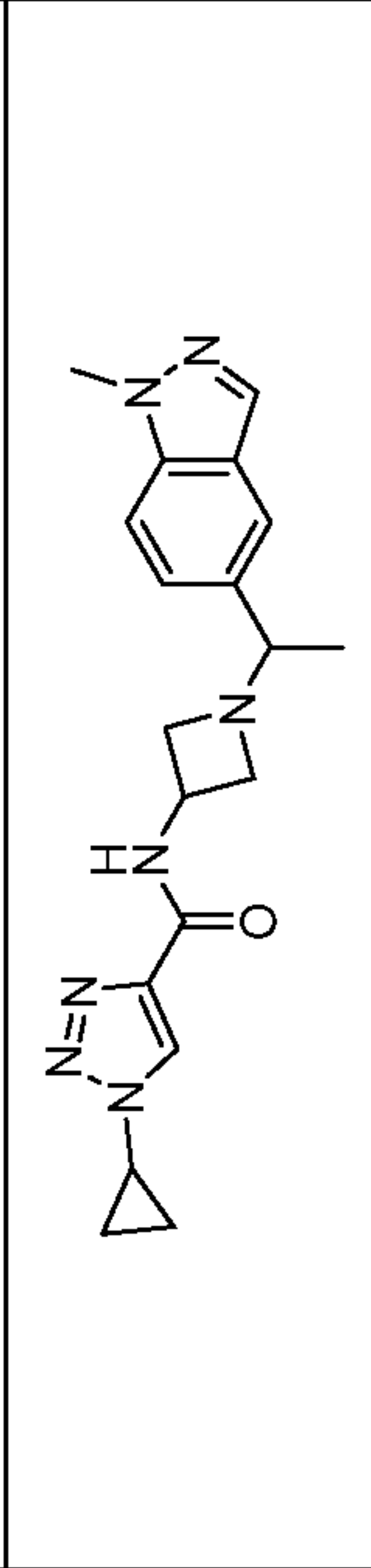
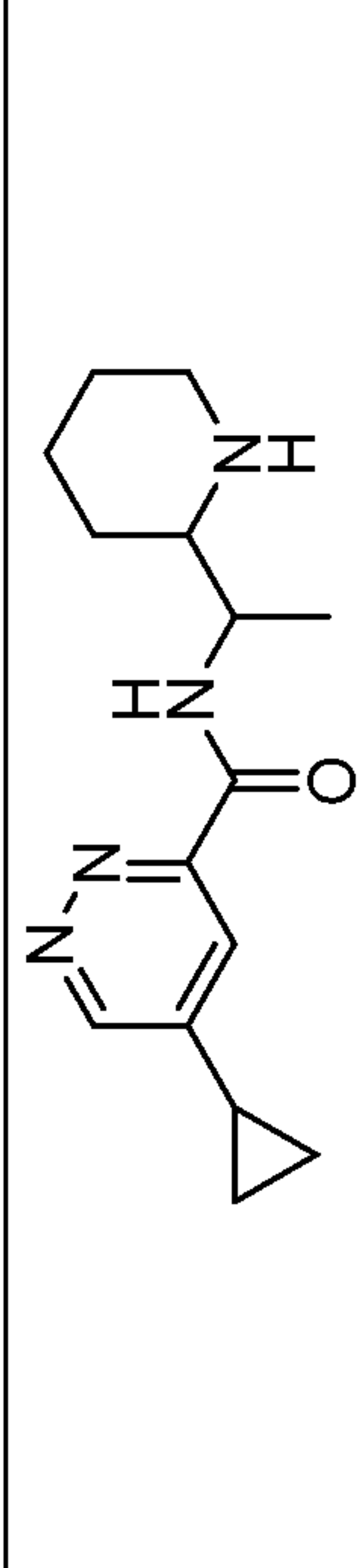
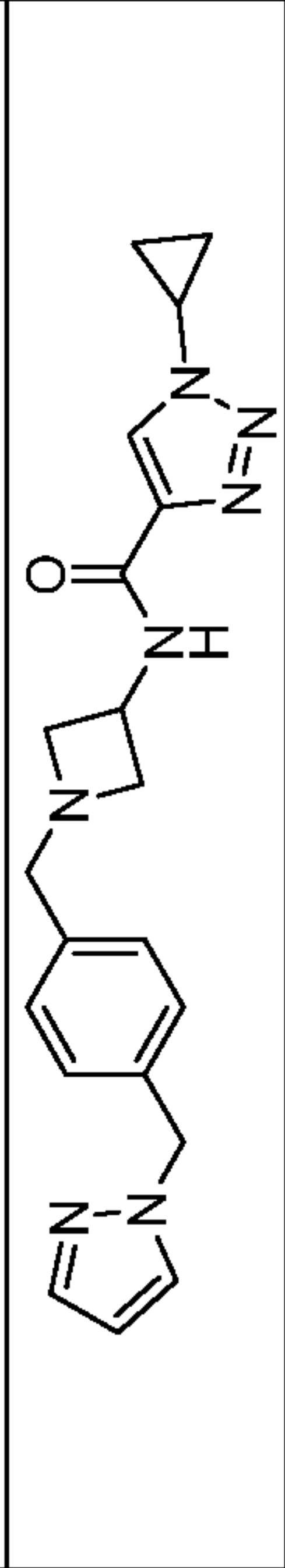
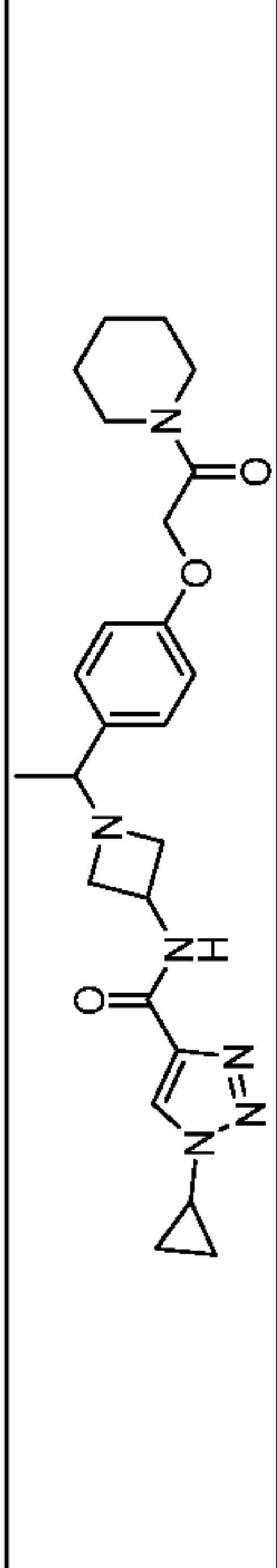
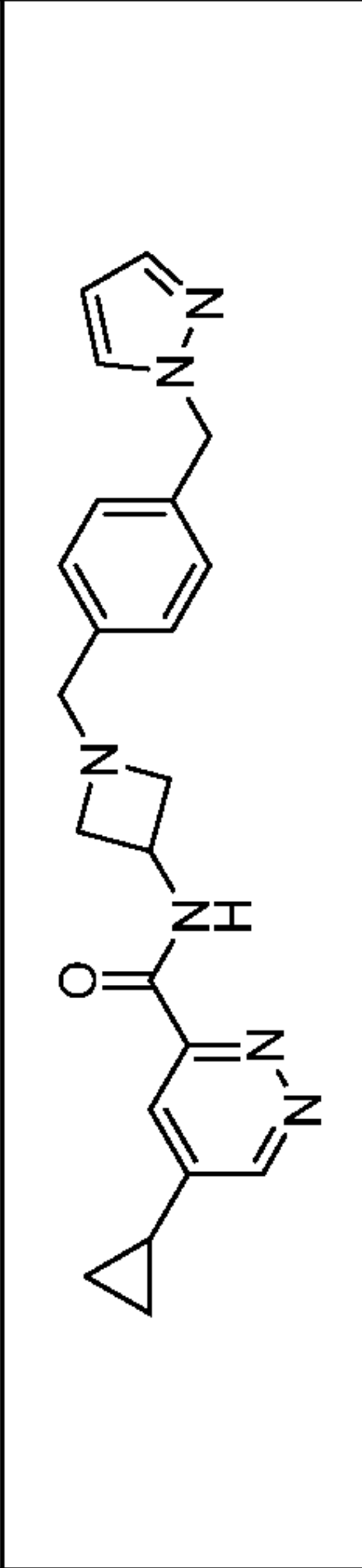
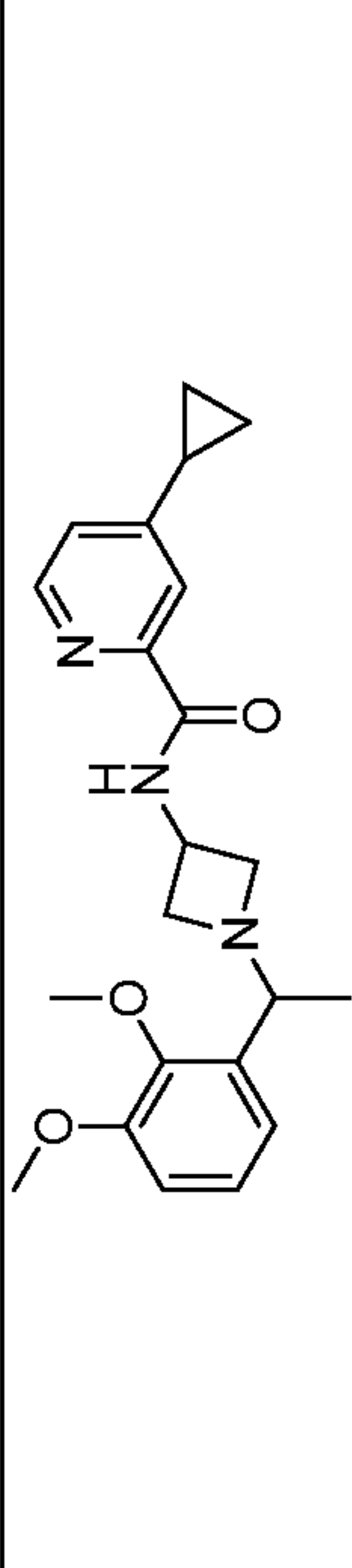
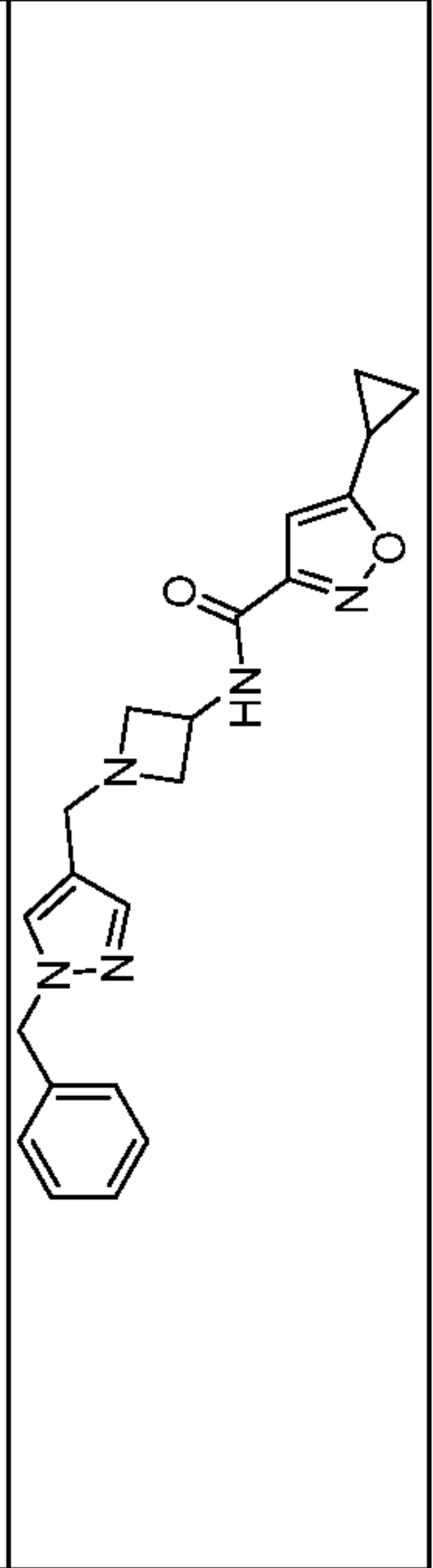
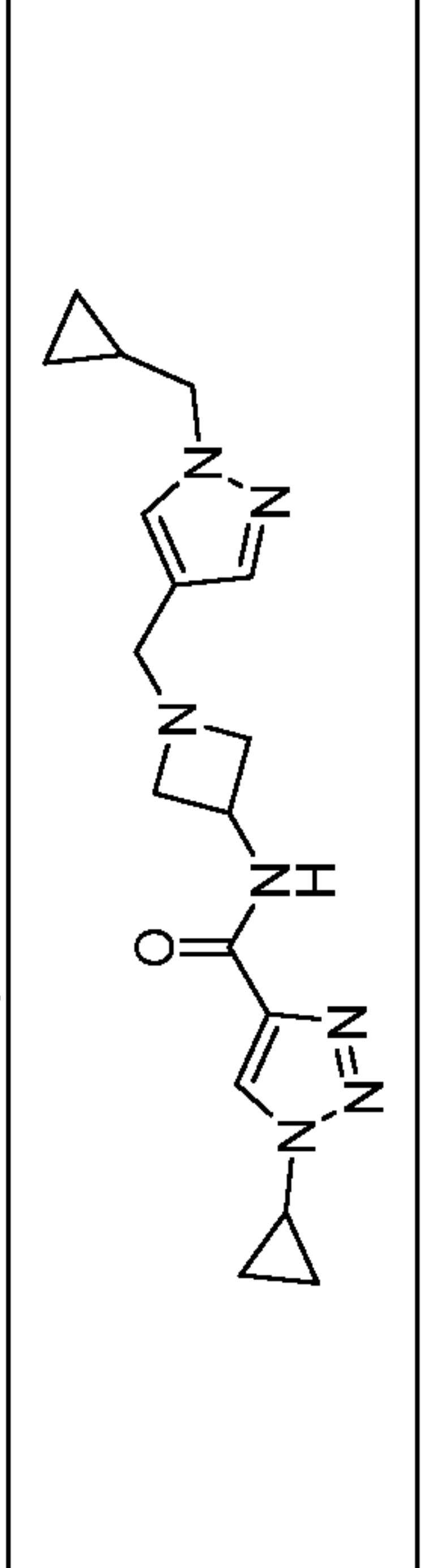
Cpd. No.	Structure	Salt Form	Cpd. No.	Structure	Salt Form
919		none	970		none
920		none	971		none
921		none	972		none
922		none	973		none
923		none	974		none
924		none	975		none

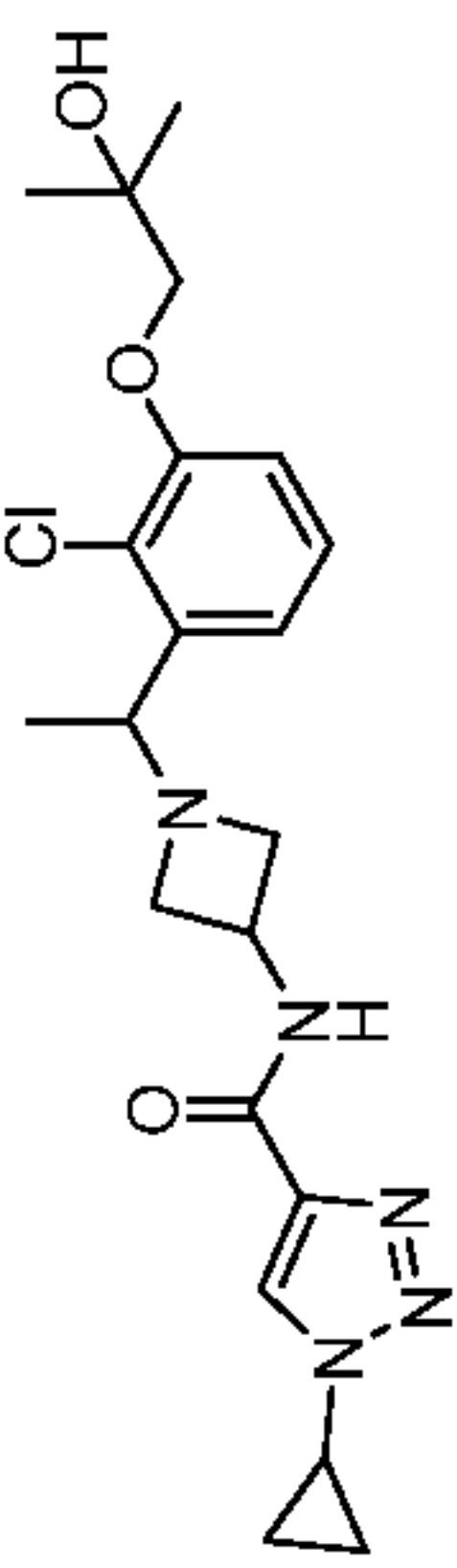
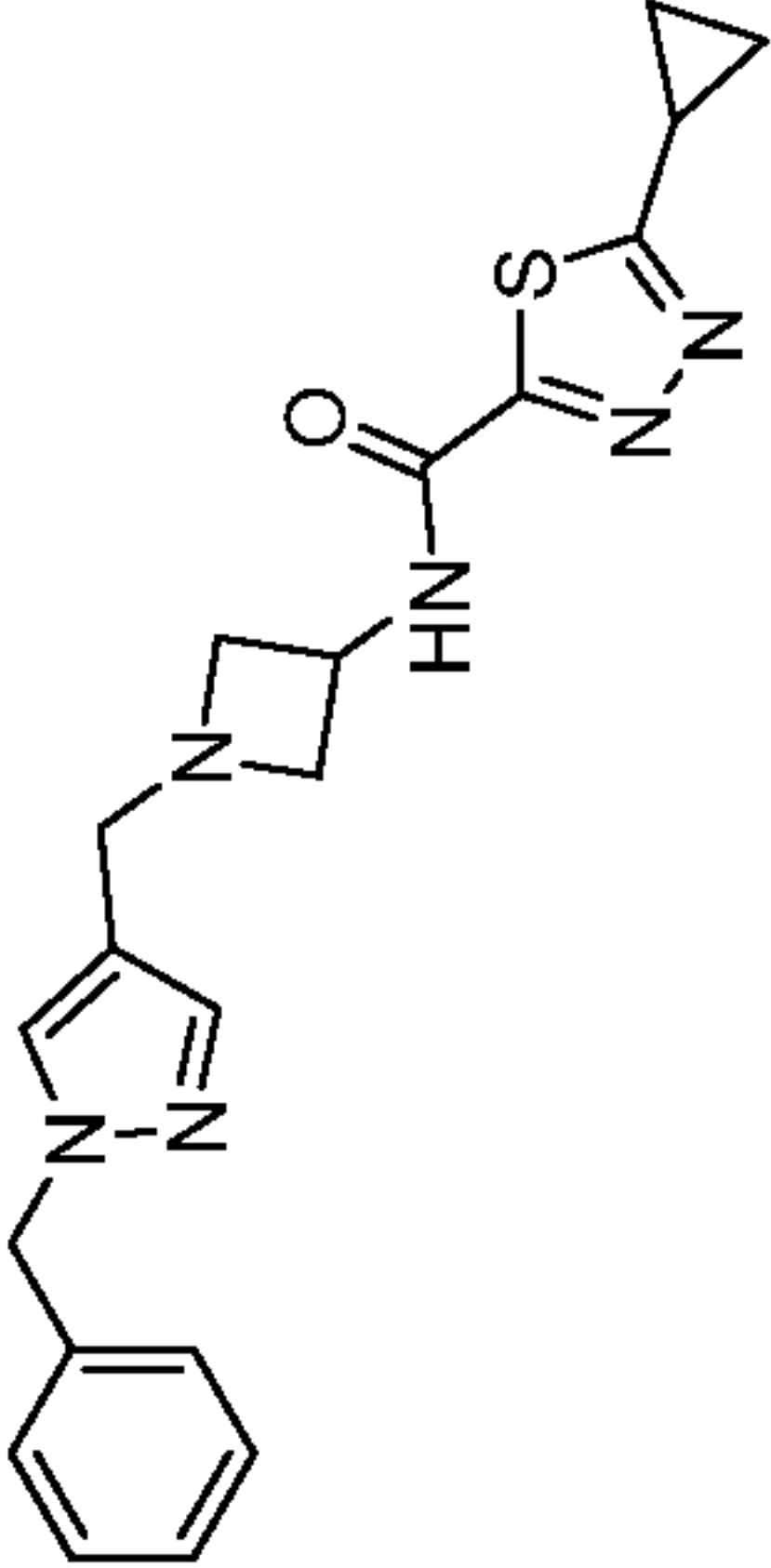
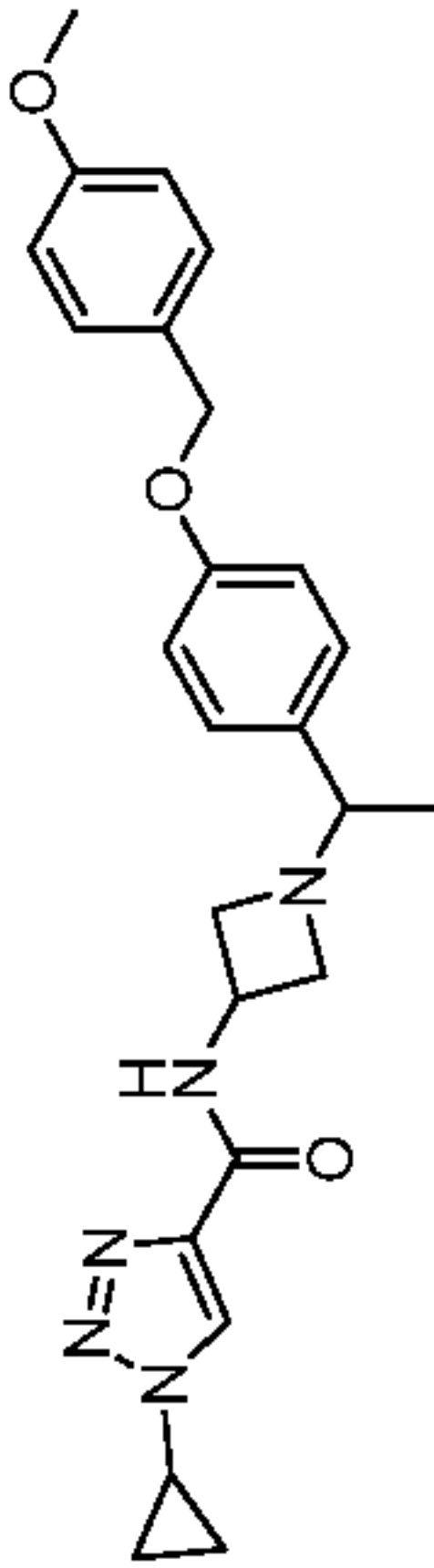
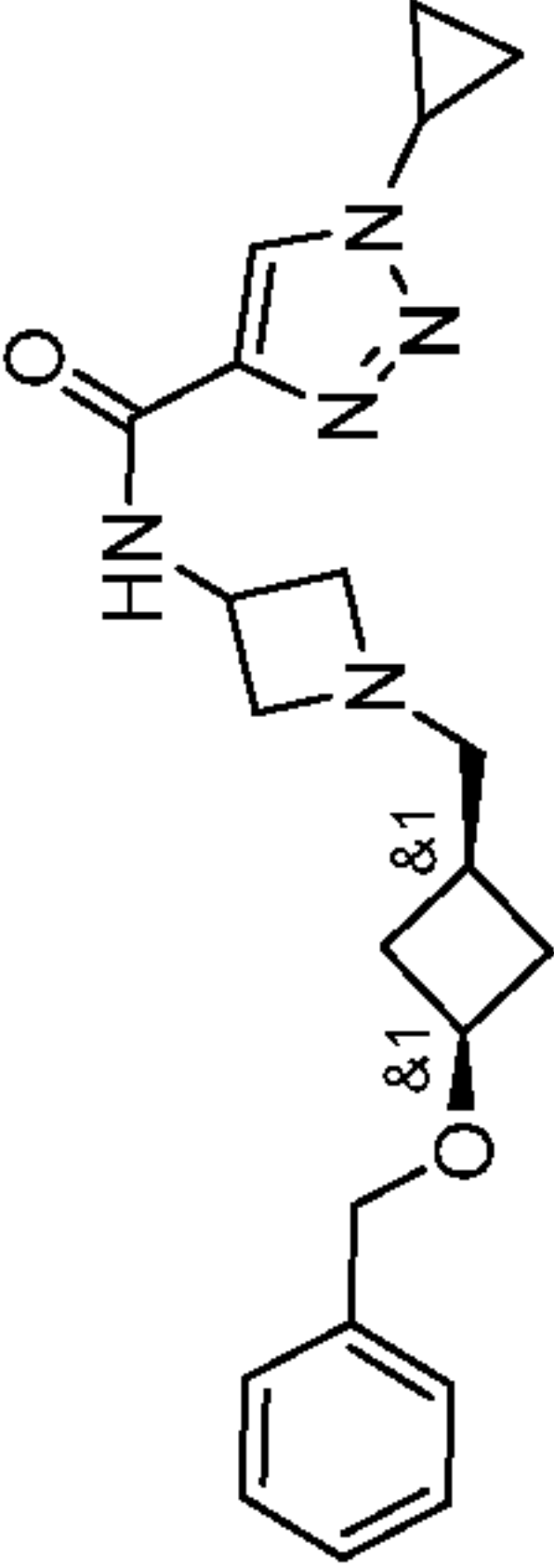
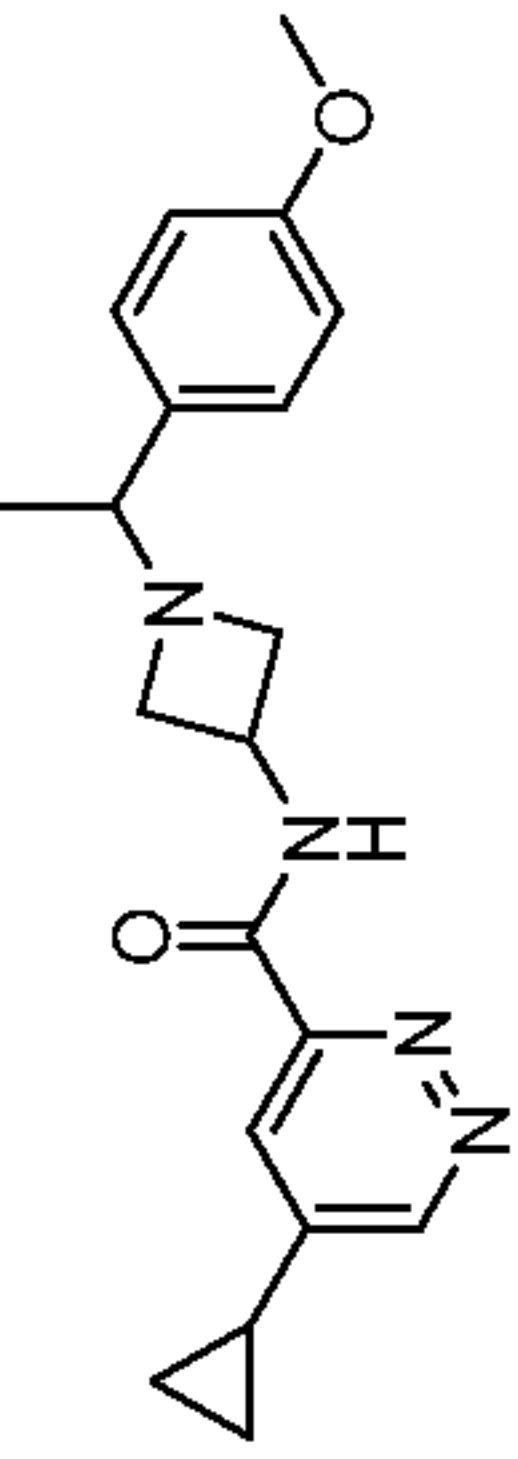
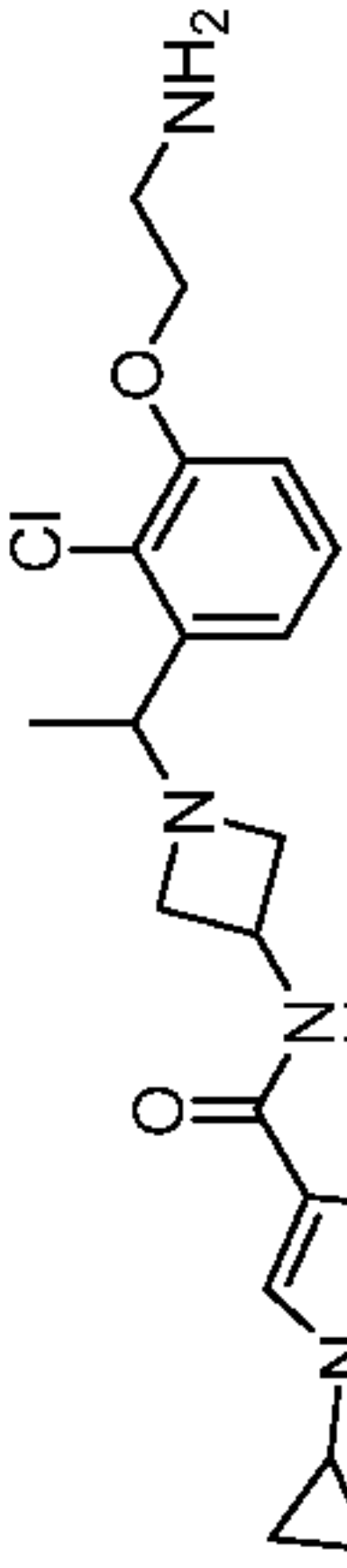
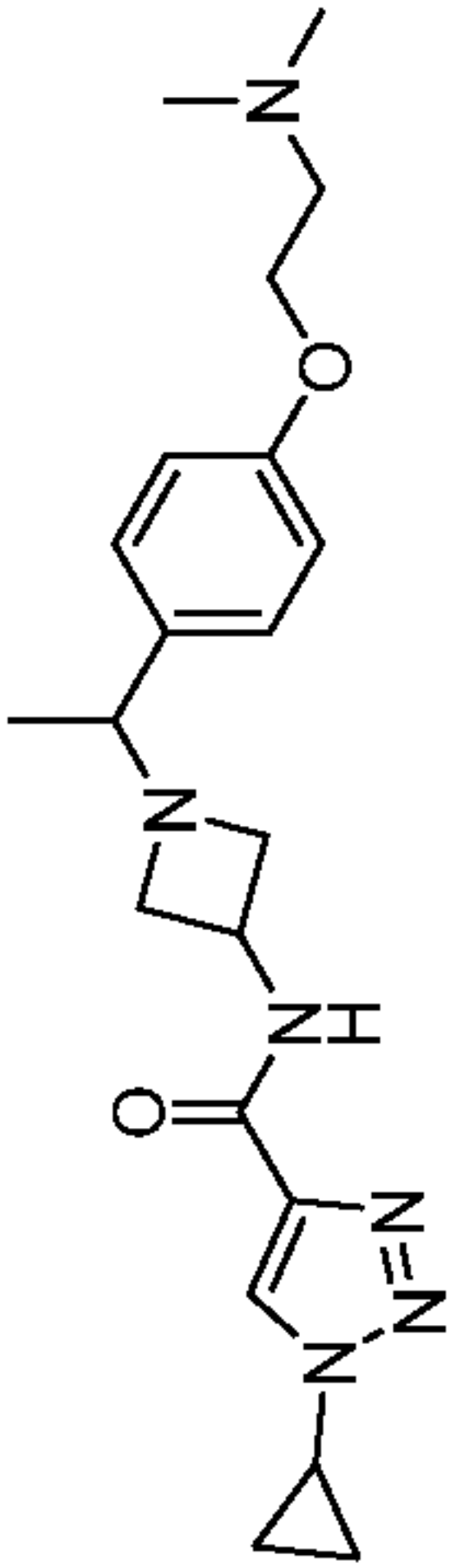
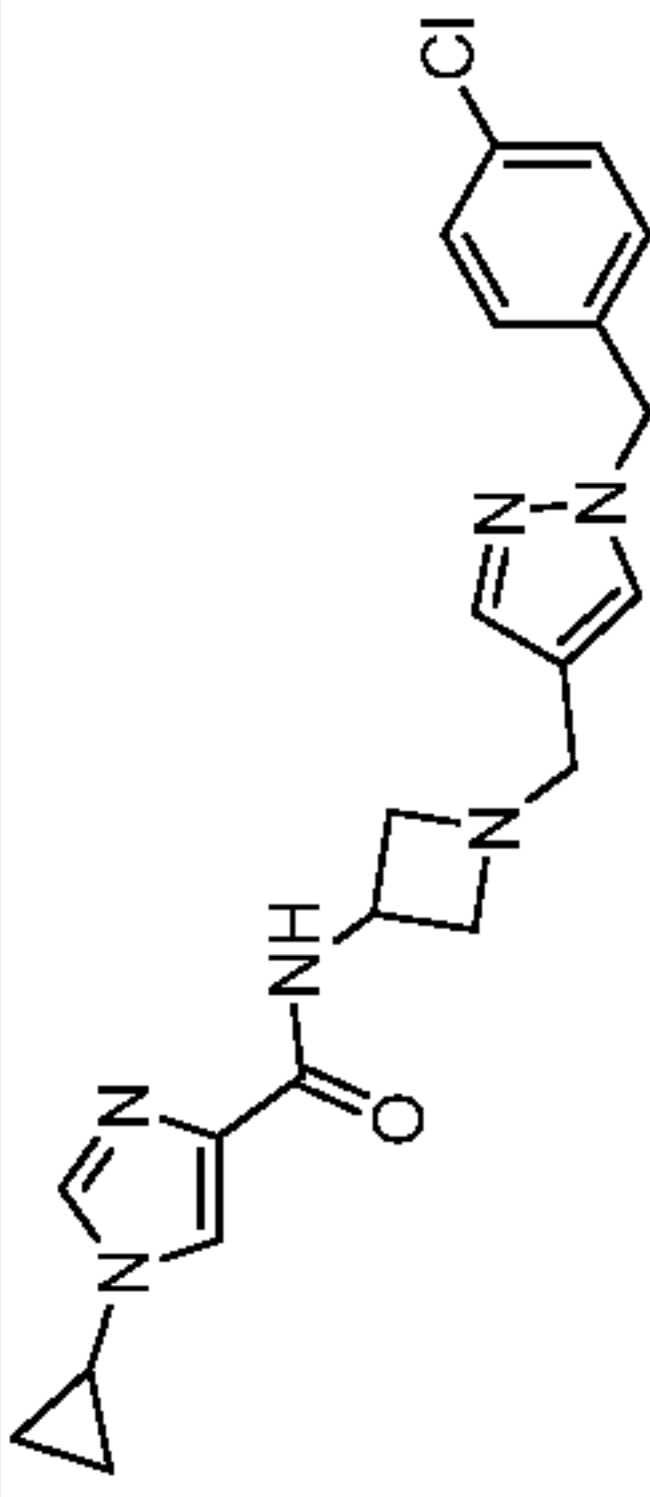
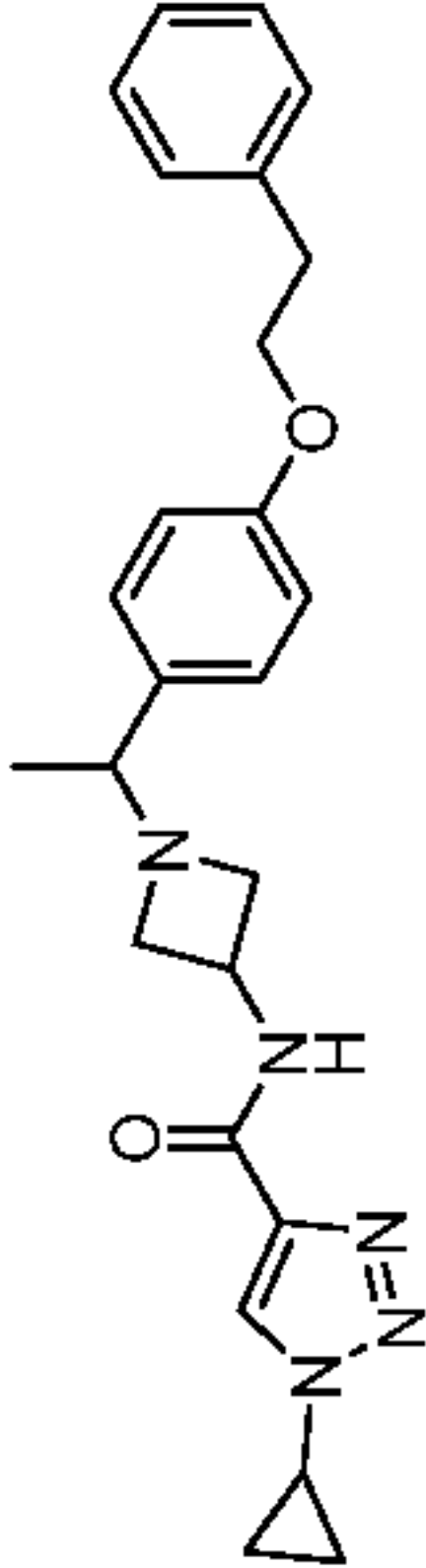
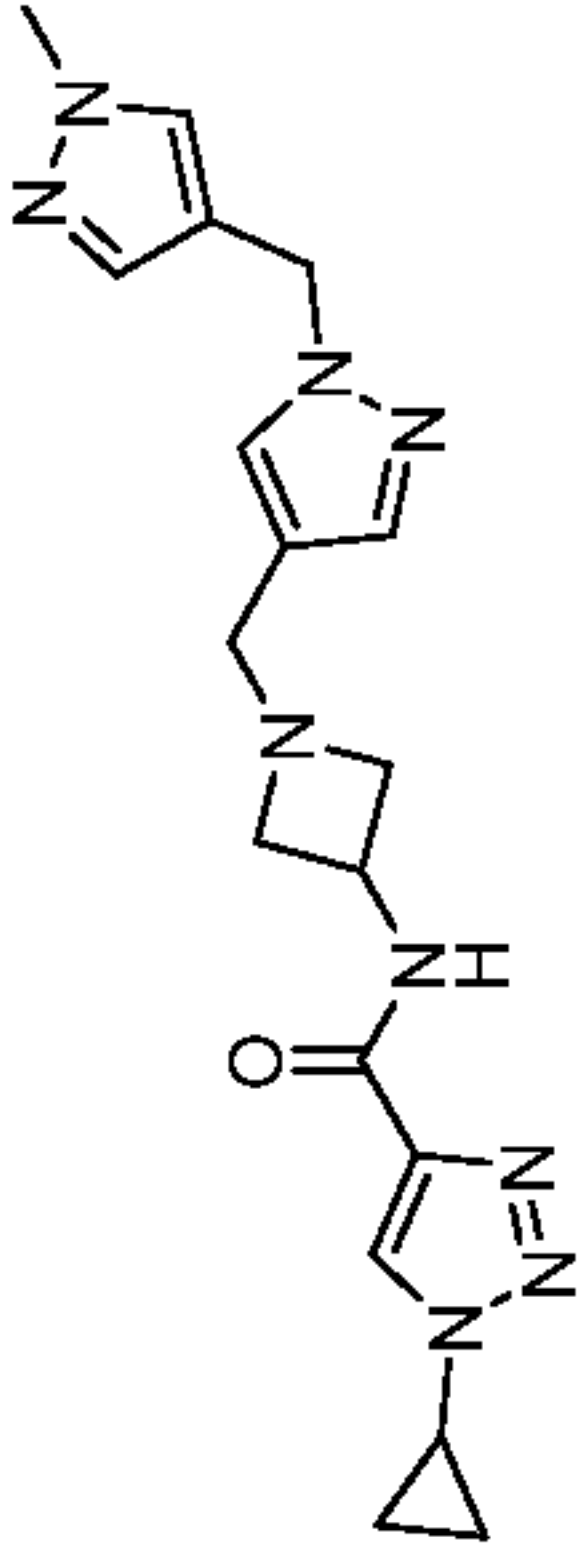
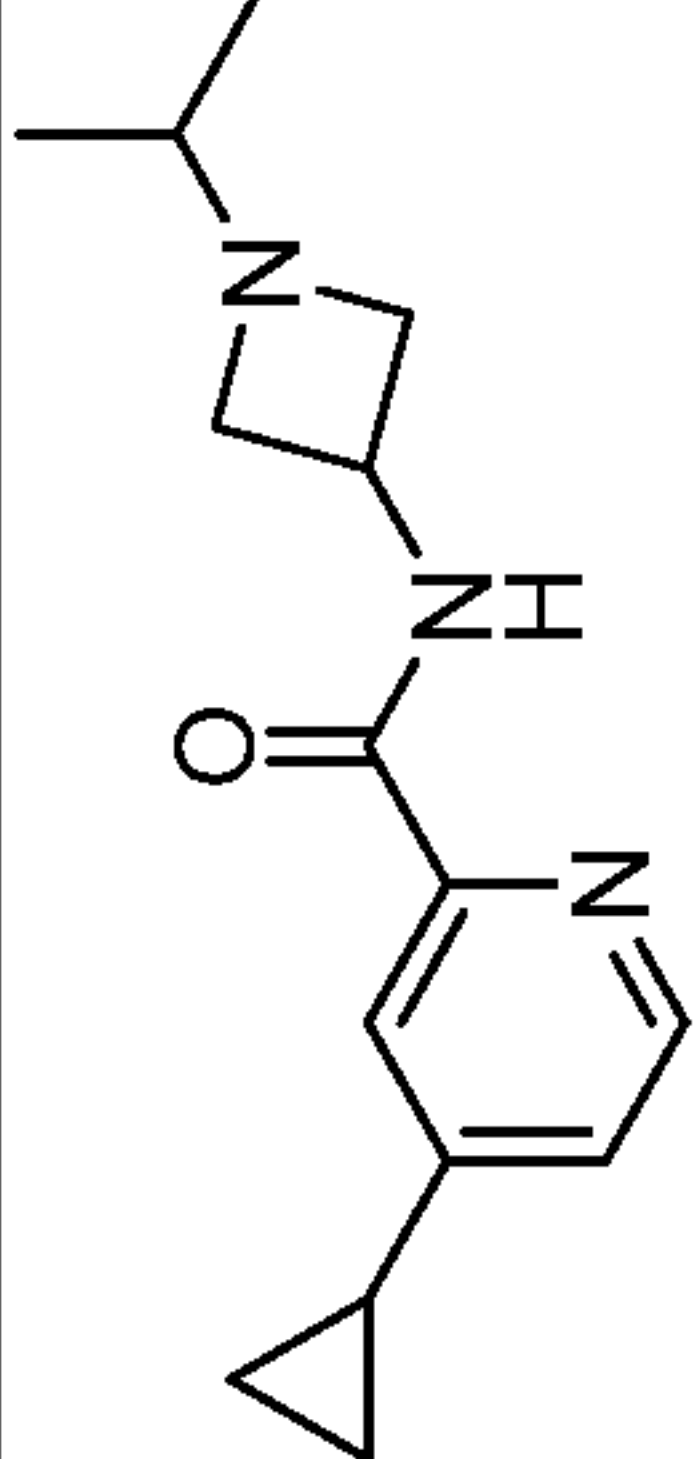
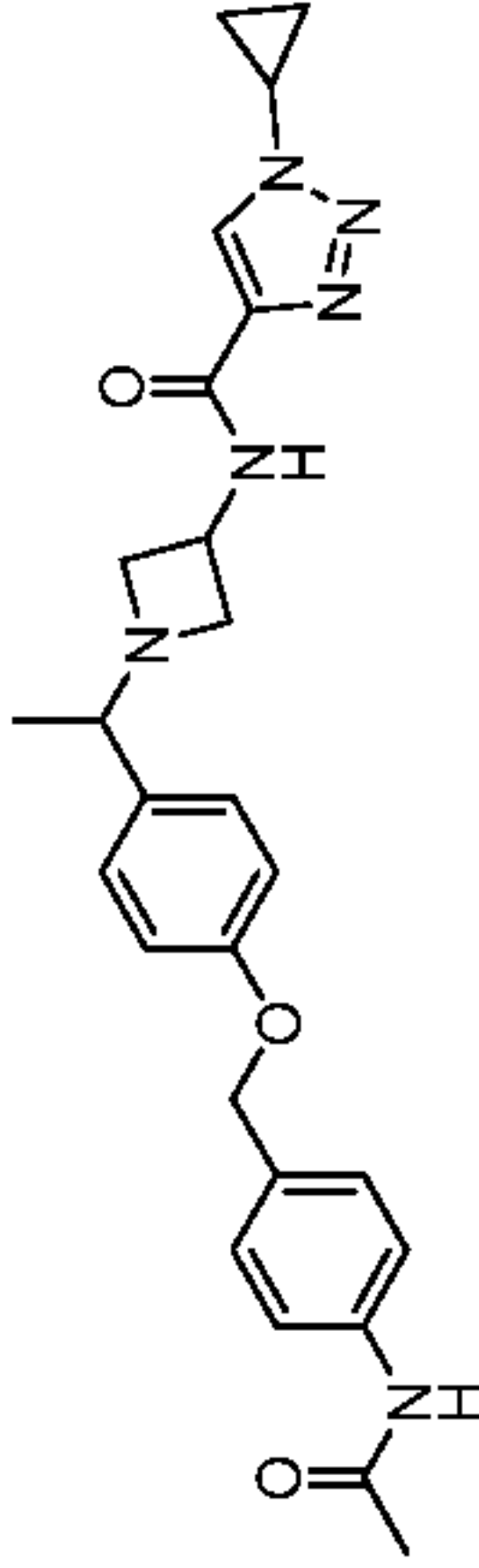
925		none	926		none
927		none	928		none
929		none	930		none
931		none	976		none
		none	977		none
		none	978		none
		none	979		none
		none	980		none
		none	981		none
		none	982		none

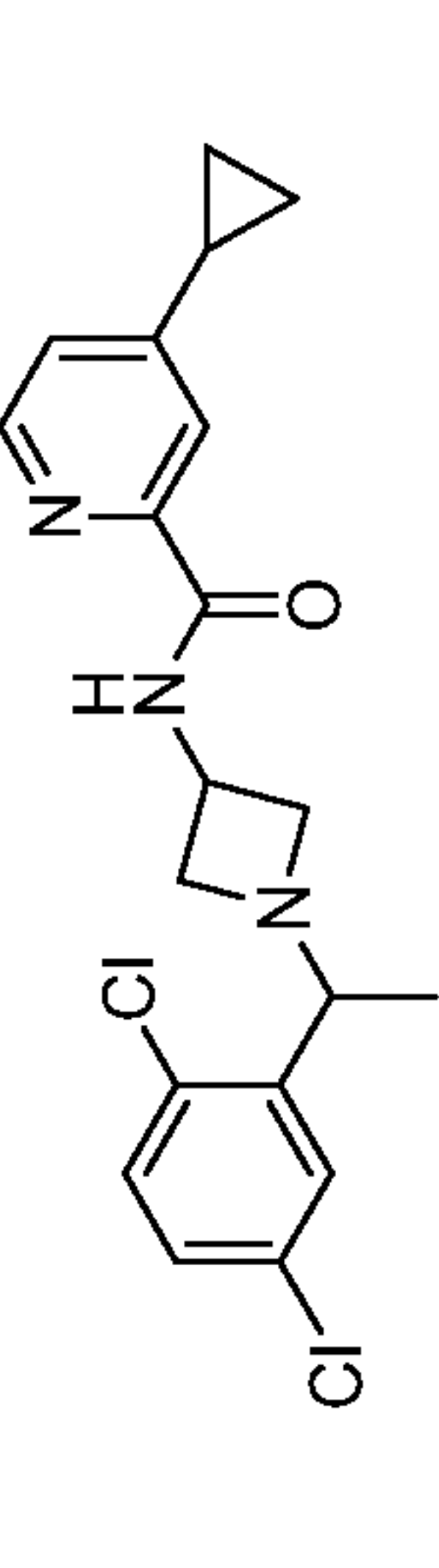
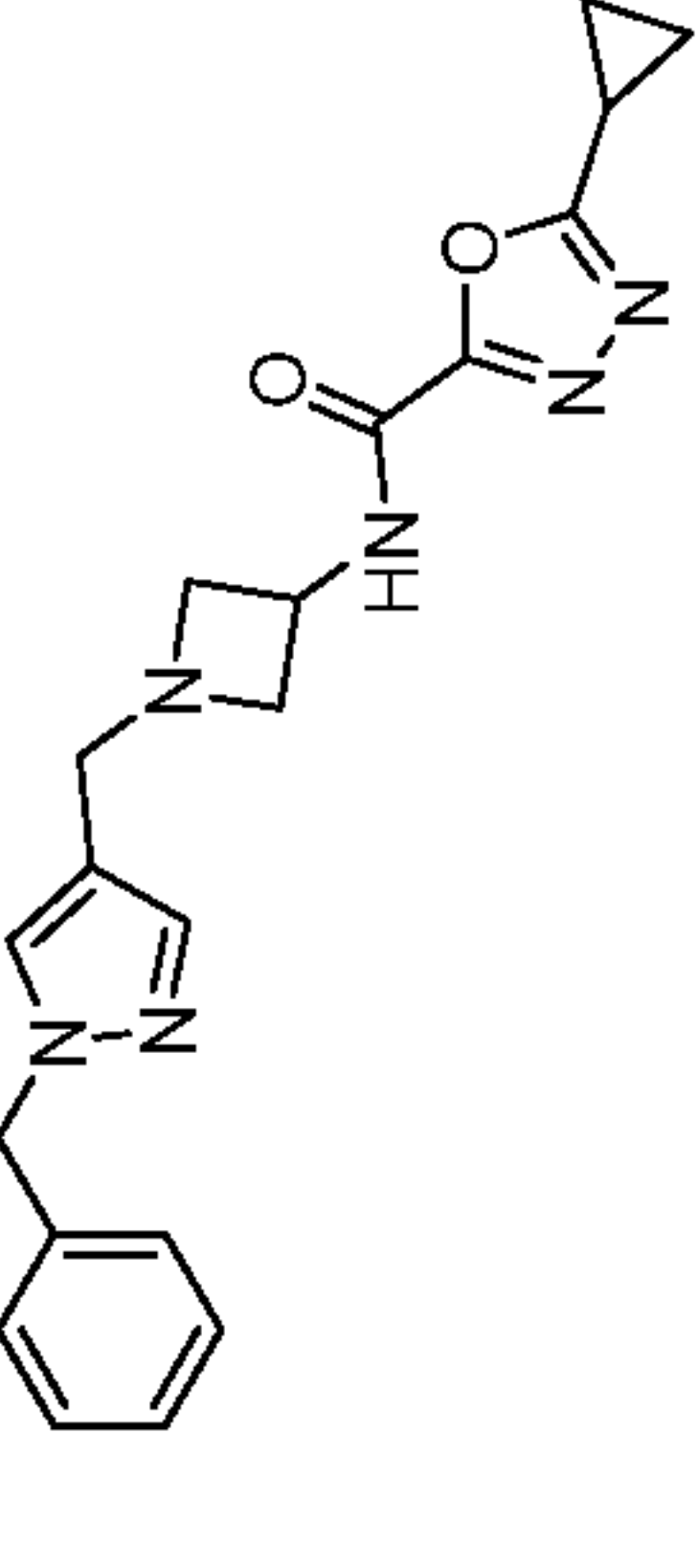
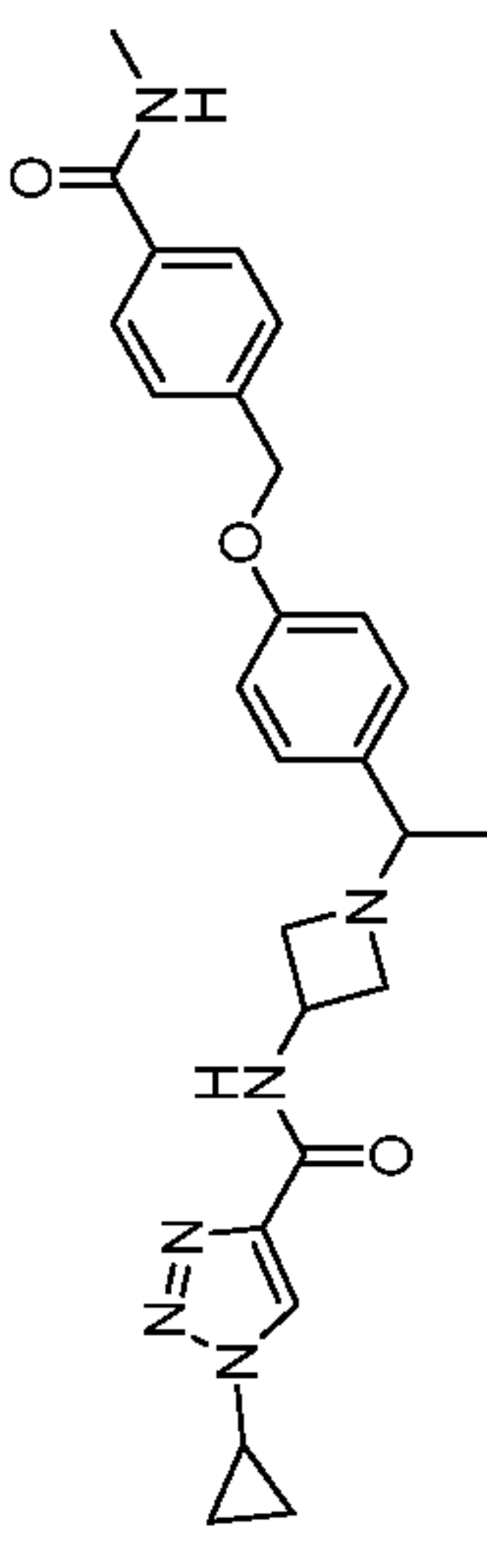
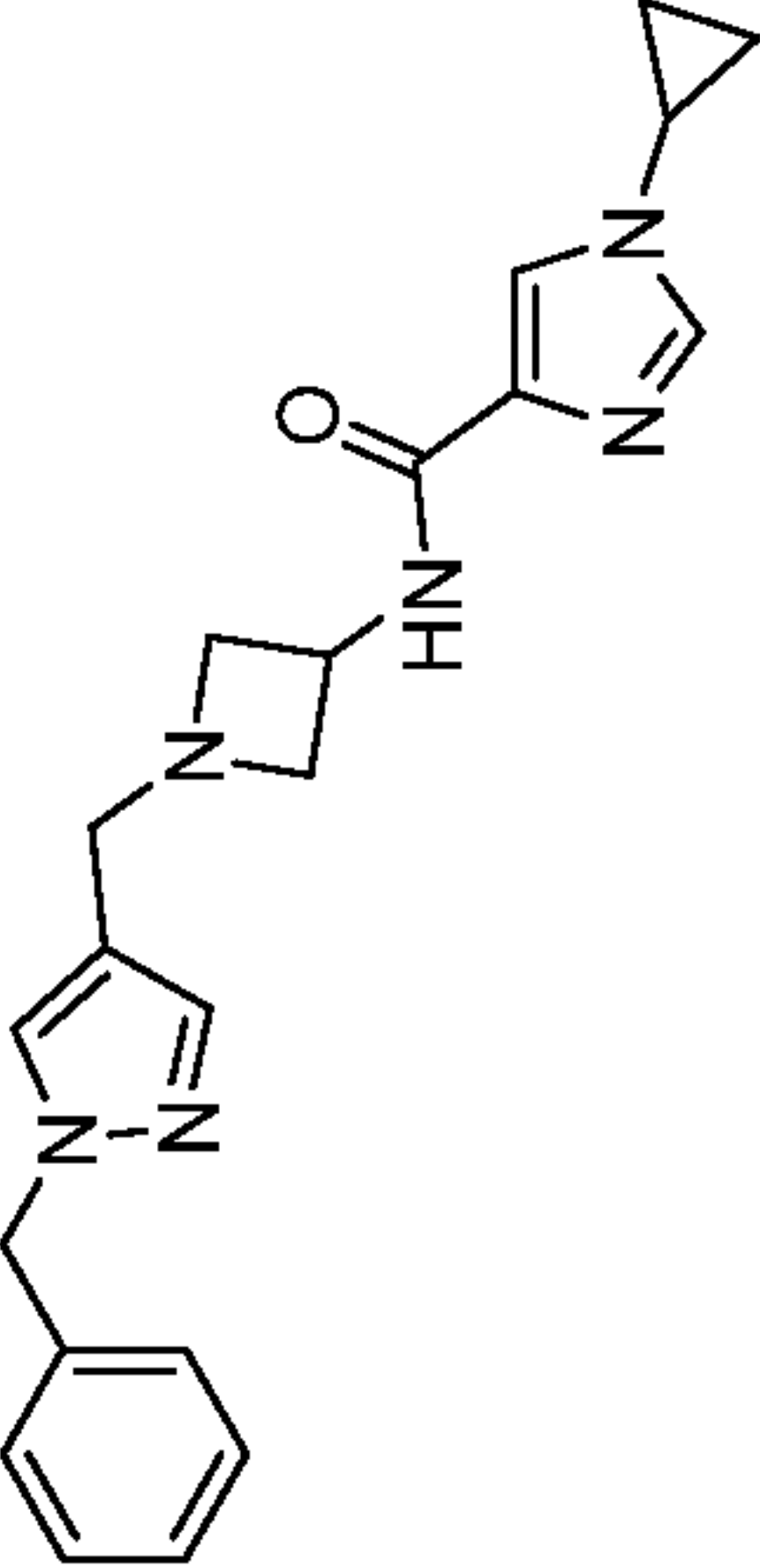
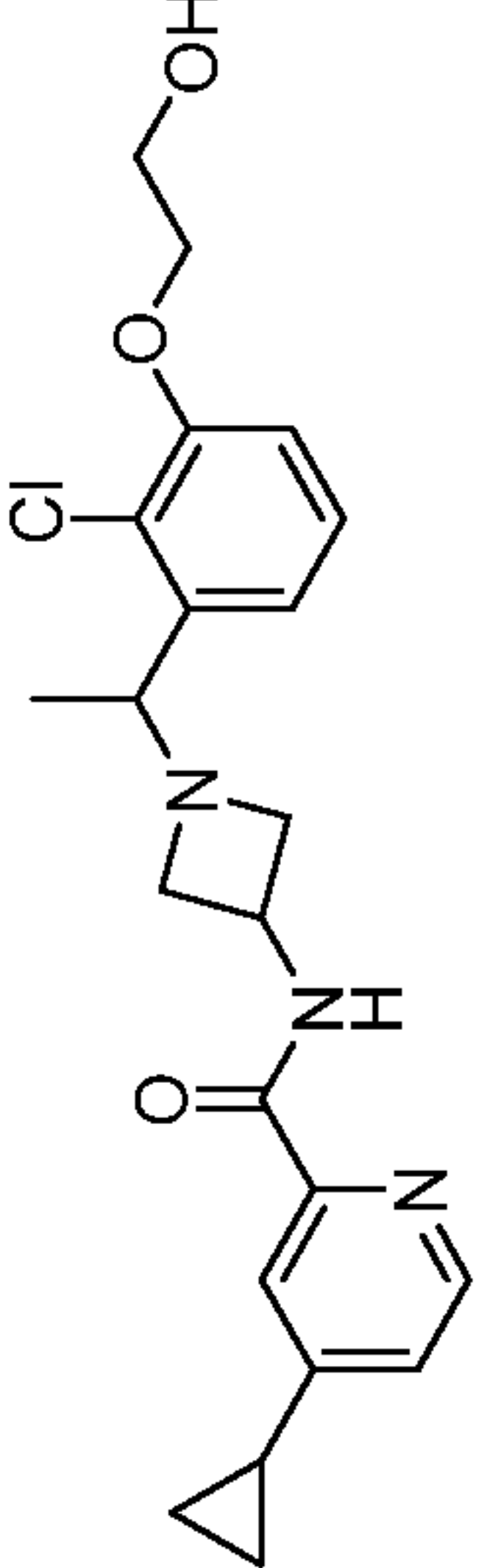
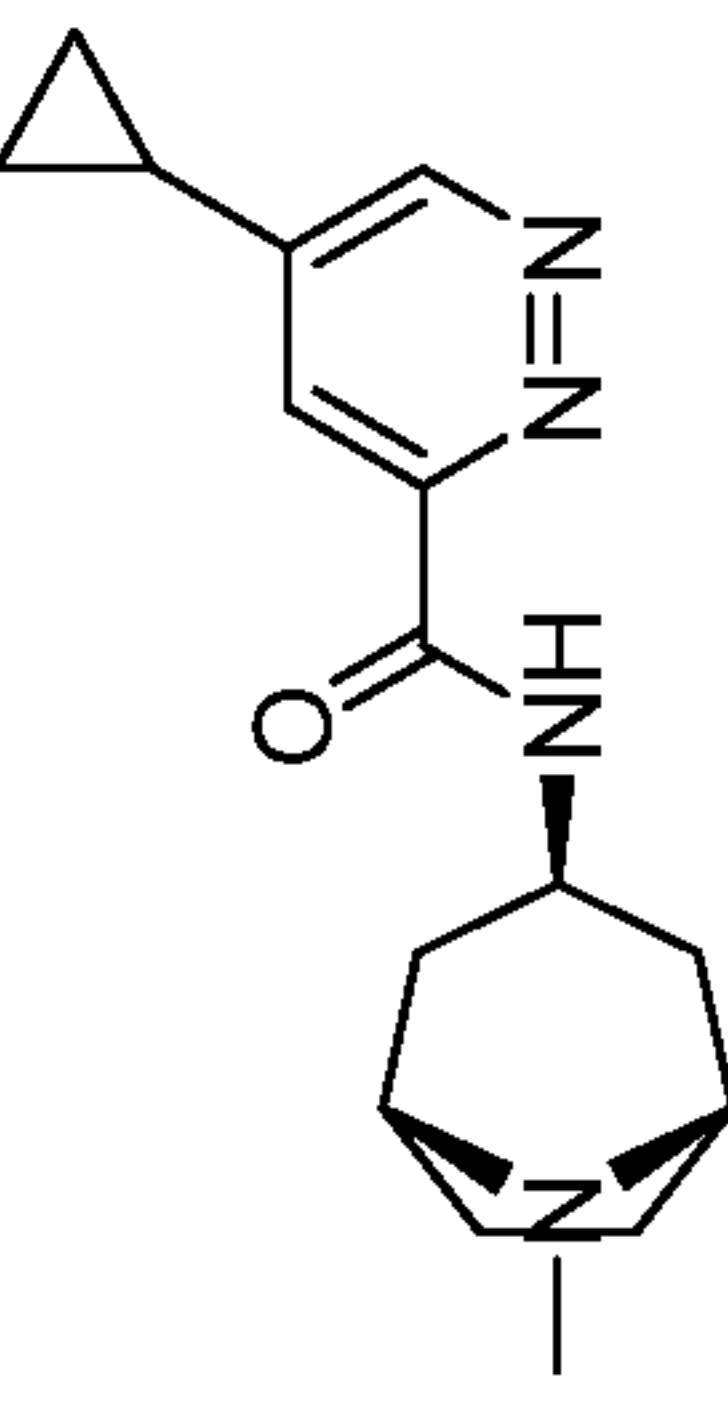
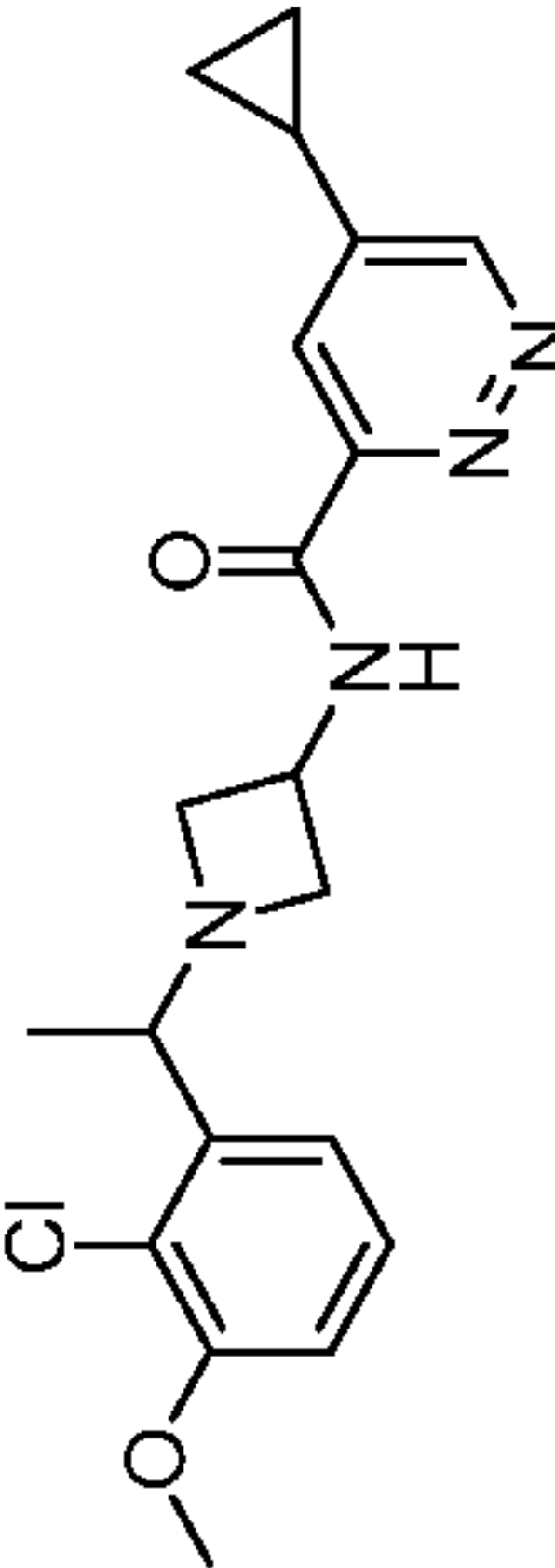
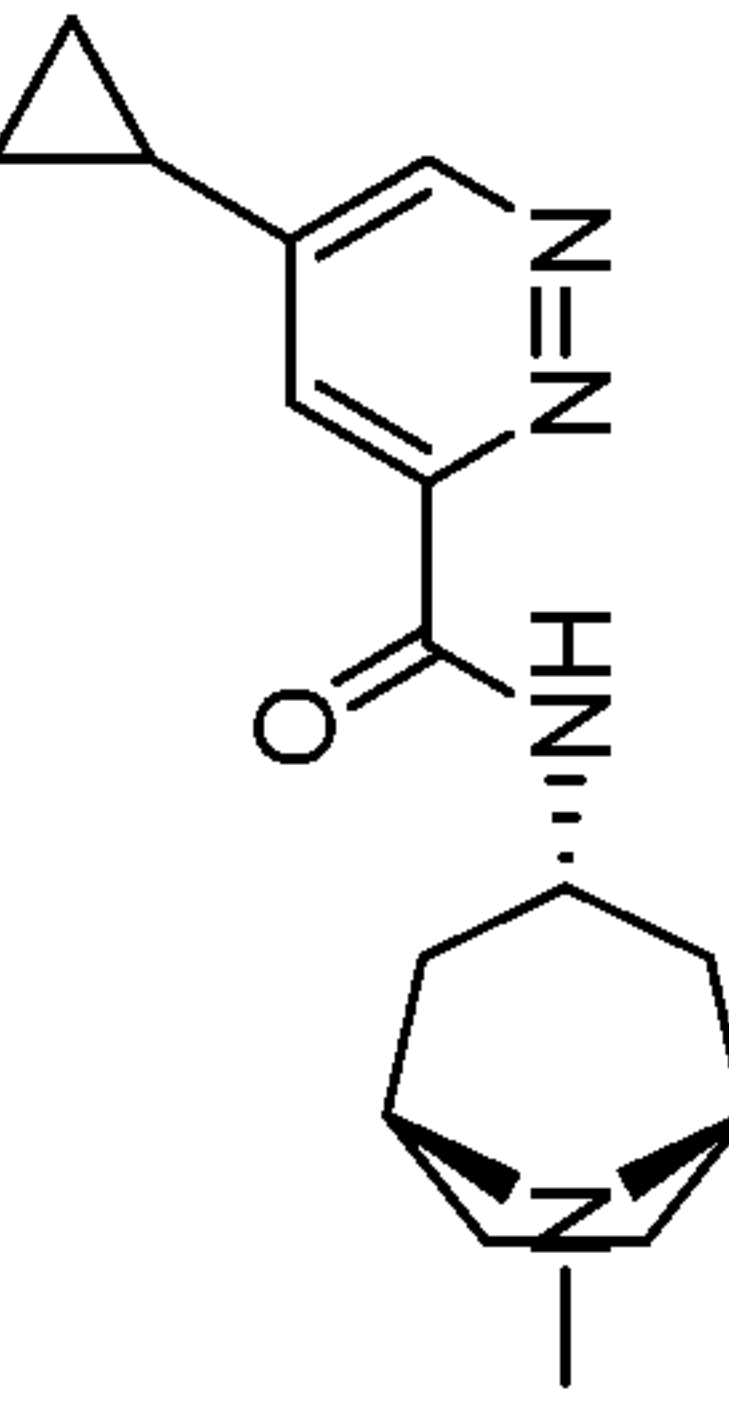
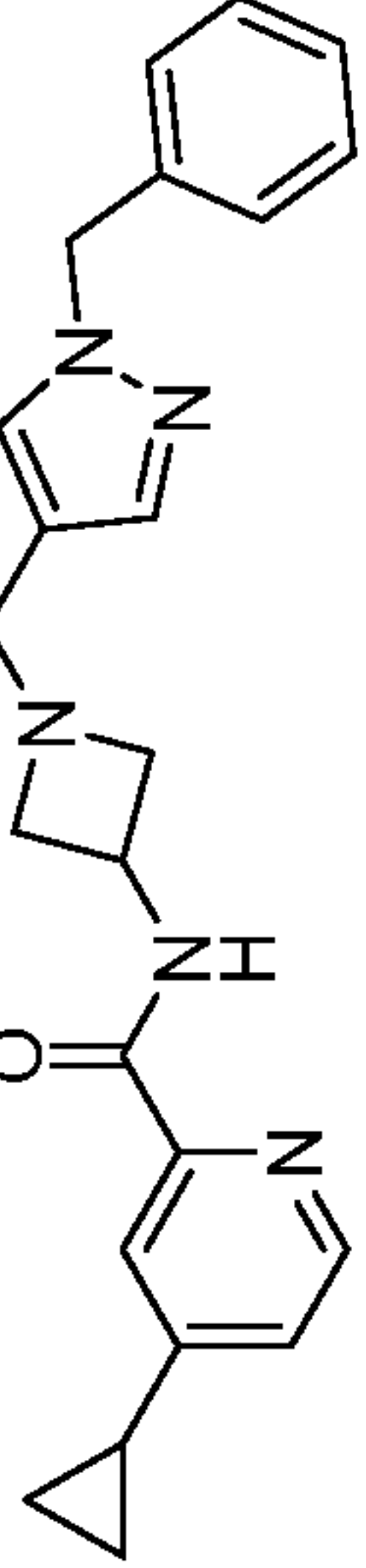
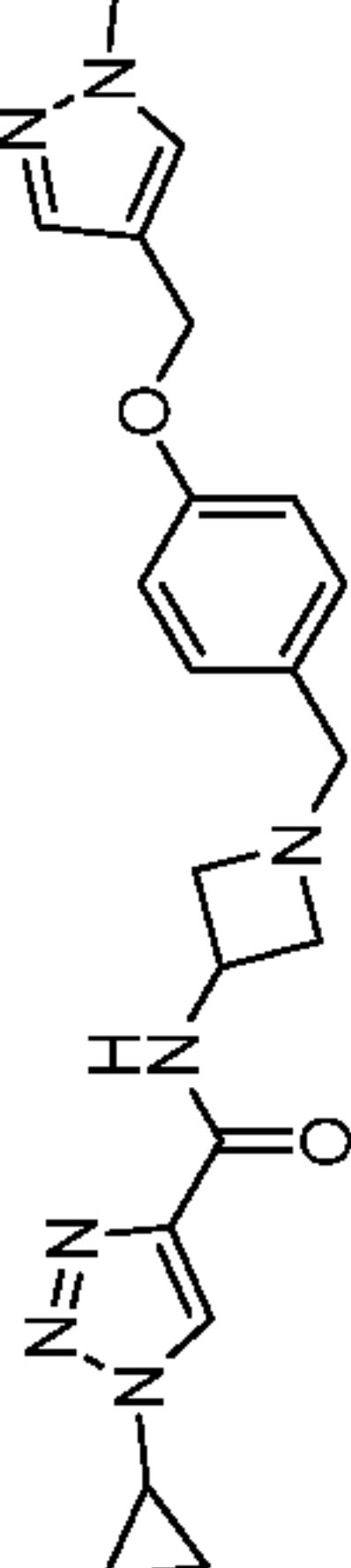
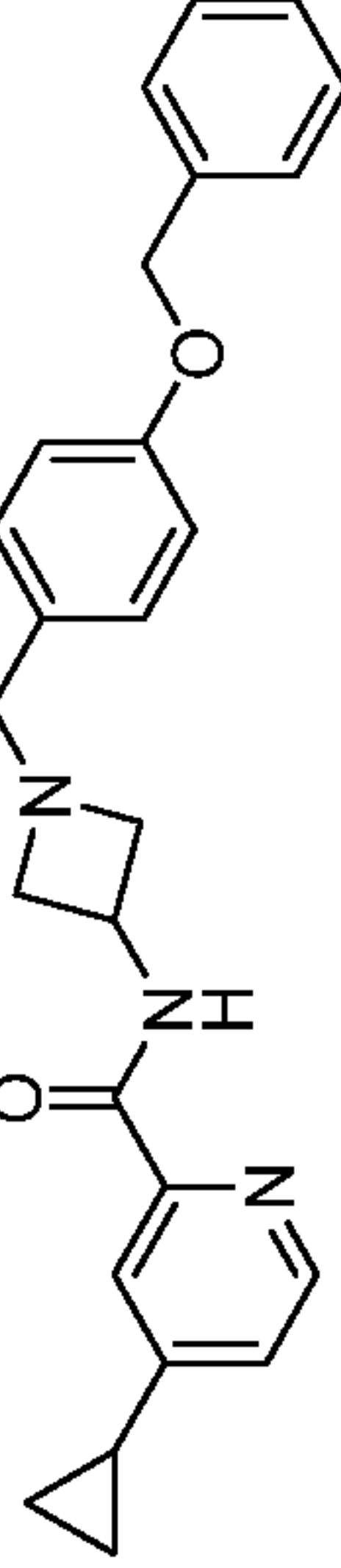
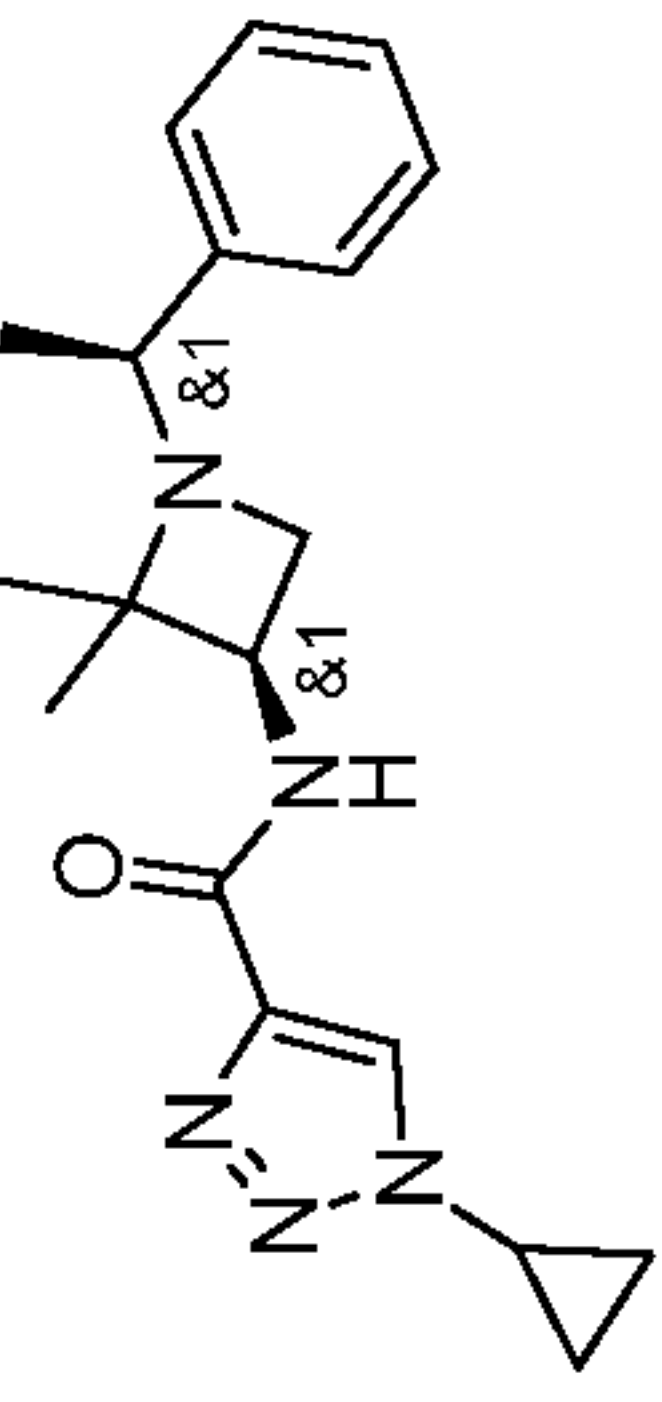
932		none	983		none
933		none	984		none
934		none	985		none
935		none	986		none
936		none	987		none
937		none	988		none

938		none	989		none
939		none	990		none
940		none	991		none
941		none	992		none
942		none	993		none
943		none	994		none

944		none	995		none
945		none	996		none
946		none	997		none
947		none	998		none
948		none	999		none
949		none	1000		none

950		none	1001		none
951		none	1002		none
952		none	1003		none
953		none	1004		none
954		none	1005		none
955		none	1006		none

956		none	1007		none
957		none	1008		none
958		none	1009		none
959		none	1012		none
960		none	1017		none
961		none	1020		none

962		none	1021		none
963		none	1022		none
964		none	1023		none
965		none	1024		none
966		none	1025		none
967		none	1026		none

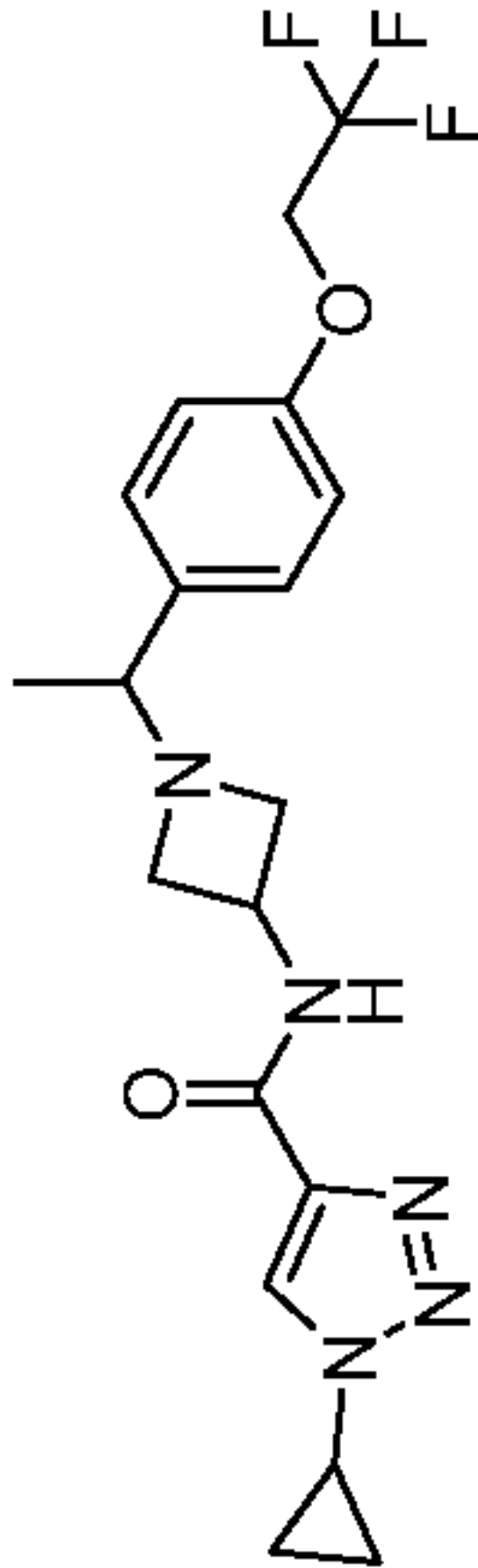
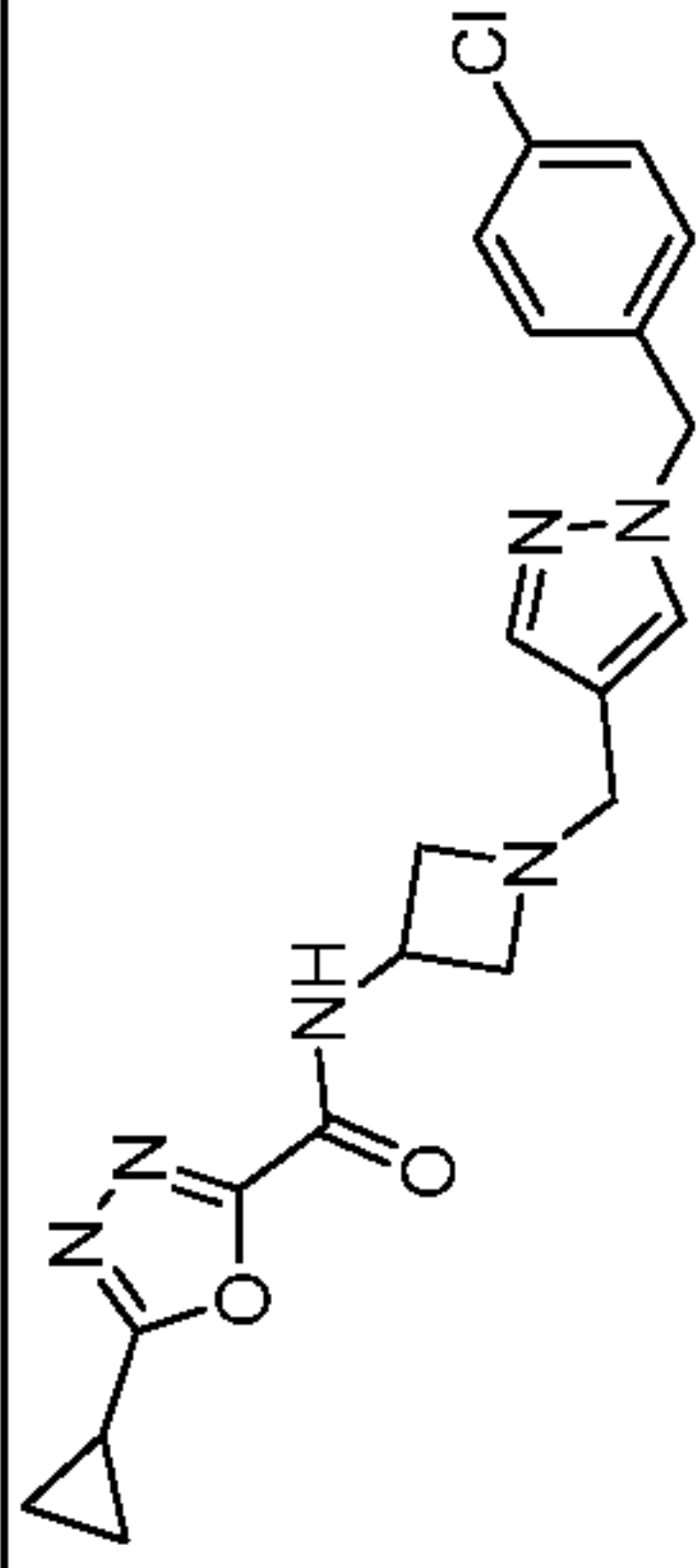
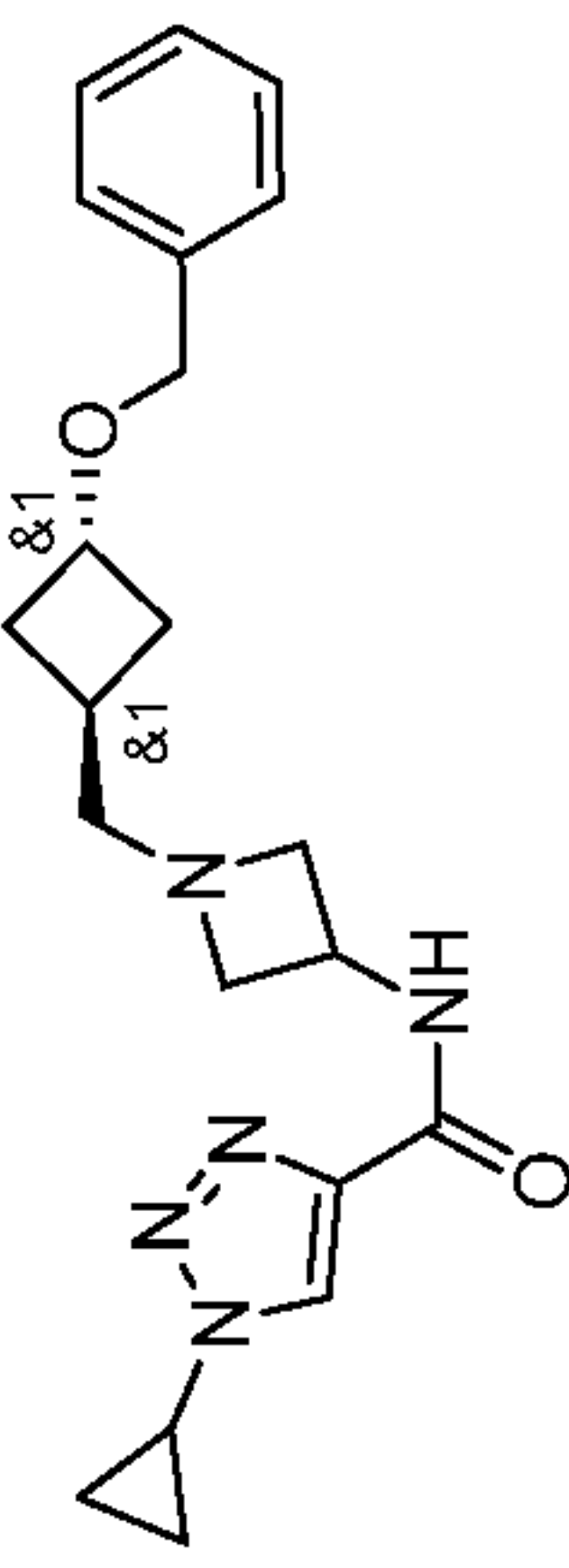
968		none	1028		none
969		none			

Table 1A

Cpd. No.	Chemical Name	LCMS M+H	SMYD3 Biochem IC ₅₀ (μM)*	SMYD3 Cell IC ₅₀ (μM)*
3	N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)nicotinamide	403.2	> 100	
4	N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)isonicotinamide	403.2	> 100	
5	N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)pyrazine-2-carboxamide	404.2	> 100	
6	N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)-1H-pyrazole-3-carboxamide	392.3	> 100	
7	N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)-1-methyl-1H-pyrazole-5-carboxamide	406.3	> 100	
8	N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)-1-methyl-1H-pyrazole-4-carboxamide	406.3	> 100	
9	N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)-1-methyl-1H-imidazole-4-carboxamide	406.3	60.5	
10	N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	433.2	16.98	
11	N-((1r,4r)-4-aminocyclohexyl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	250	15.37	
12	N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)-1-(cyclopropylmethyl)piperidine-4-carboxamide	463	45.94	
13	N-((1r,4r)-4-aminocyclohexyl)-1-ethyl-1H-pyrazole-3-carboxamide	237.1	112.37	
14	N-((1r,4r)-4-aminocyclohexyl)-3-ethylisoxazole-5-carboxamide	238.15	104.43	
15	N-((1r,4r)-4-aminocyclohexyl)-1-ethyl-1H-imidazole-4-carboxamide	237.1	56.59	
16	N-((1r,4r)-4-aminocyclohexyl)-2-ethyloxazole-4-carboxamide	NA	128.43	
17	N-((1r,4r)-4-aminocyclohexyl)-5-ethylisothiazole-3-carboxamide	254.1	13.52	
18	N-((1r,4r)-4-aminocyclohexyl)-4-ethylbenzamide	247.1	125.3	

19	N-((1r,4r)-4-aminocyclohexyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboxamide	289.9	102.25	
20	N-((1r,4r)-4-aminocyclohexyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide	289.8	16.03	
21	N-((1r,4r)-4-aminocyclohexyl)-3-ethylbenzamide	247.3	57.46	
22	N-((1r,4r)-4-aminocyclohexyl)-5-ethylnicotinamide	247.9	31.29	
23	3-acetyl-N-((1r,4r)-4-aminocyclohexyl)benzamide	261.2	91.55	
24	3-acetamido-N-((1r,4r)-4-aminocyclohexyl)benzamide	276.2	80.28	
25	N-((1r,4r)-4-aminocyclohexyl)-3-propionamidobenzamide	290.2	84.27	
26	N-((1r,4r)-4-aminocyclohexyl)-3-(hydroxymethyl)benzamide	248.9	86.01	
27	N-((1r,4r)-4-aminocyclohexyl)-1-ethyl-3-methyl-1H-pyrazole-5-carboxamide	251.2	101.58	
28	N-((1r,4r)-4-aminocyclohexyl)-3-methyl-1-phenyl-1H-pyrazole-5-carboxamide	299.25	110.89	
29	N-((1r,4r)-4-aminocyclohexyl)-1-benzyl-3-methyl-1H-pyrazole-5-carboxamide	313.2	13.99	
30	1-ethyl-3-methyl-N-(phenyl(piperidin-4-yl)methyl)-1H-pyrazole-5-carboxamide	327.15	69.19	
31	3-methyl-1-phenyl-N-(phenyl(piperidin-4-yl)methyl)-1H-pyrazole-5-carboxamide	375.2	56.66	
32	1-benzyl-3-methyl-N-(phenyl(piperidin-4-yl)methyl)-1H-pyrazole-5-carboxamide	389.25	91.27	
33	N-(4-(aminomethyl)phenyl)-6-hydroxypyridazine-3-carboxamide	228.05 (-NH ₂)	130.63	
34	N-(4-(aminomethyl)phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide	282.1 (-NH ₂)	153.36	
35	N-(4-(aminomethyl)phenyl)-1-ethyl-3-methyl-1H-pyrazole-5-carboxamide	242.05 (-NH ₂)	124.89	
36	N-(4-(aminomethyl)phenyl)-3-methyl-1-phenyl-1H-pyrazole-5-carboxamide	290.15 (-NH ₂)	123.93	
37	N-((1r,4r)-4-aminocyclohexyl)-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide	251.34	59.91	
38	N-((1r,4r)-4-aminocyclohexyl)-4-ethylpicolinamide	248	20.5	
39	2-oxo-N-(piperidin-4-yl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide	274.9	23.86	
40	N-((1r,4r)-4-aminocyclohexyl)-2-oxoindoline-5-carboxamide	274.1	2.84	

42	N-((1r,4r)-4-aminocyclohexyl)-2-oxoindoline-5-carboxamide	274.2	3.31	
43	N-((1r,4r)-4-aminocyclohexyl)-2-hydroxyquinoxaline-6-carboxamide	287	60.36	
44	2-oxo-N-(phenyl(piperidin-4-yl)methyl)indoline-5-carboxamide	350.25	14.08	
45	5-amino-N-(phenyl(piperidin-4-yl)methyl)-1H-pyrazole-3-carboxamide	300.25	137.24	
46	3-oxo-N-(piperidin-4-yl)-3,4-dihydroquinoxaline-6-carboxamide	272.9	63.74	
47	N-((1r,4r)-4-aminocyclohexyl)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carboxamide	274.8	11.94	
48	3-amino-N-((1r,4r)-4-aminocyclohexyl)-1-methyl-1H-pyrazole-5-carboxamide	237.9	117.12	
49	N-(1-(L-tyrosyl)piperidin-4-yl)-2-oxoindoline-5-carboxamide	423.3	0.86	
50	2-oxo-N-(piperidin-4-yl)indoline-5-carboxamide	260.2	12.15	
51	N-(1-(L-tryptophyl)piperidin-4-yl)-2-oxoindoline-5-carboxamide	446.4	0.69	
52	N-(4-(aminomethyl)phenyl)-4-propionyl-1H-pyrrole-2-carboxamide	272.2	107.67	
53	N-((1r,4r)-4-aminocyclohexyl)-2-butylcyclopropane-1-carboxamide	239.3	121.58	
54	N-((1r,4r)-4-aminocyclohexyl)-5-ethylthiophene-2-carboxamide	253.4	49.88	
55	5-ethyl-N-(phenyl(piperidin-4-yl)methyl)thiophene-2-carboxamide	329.2	116.27	
56	N-(4-(aminomethyl)phenyl)-5-ethylthiophene-2-carboxamide	261.1	138.14	
57	N-((1r,4r)-4-aminocyclohexyl)-2-methyl-4H-furo[3,2-b]pyrrole-5-carboxamide	261.7	134.08	
58	2-methyl-N-(piperidin-4-yl)-4H-furo[3,2-b]pyrrole-5-carboxamide	248.1	76.14	
59	N-((1r,4r)-4-aminocyclohexyl)-2-ethylthiazole-5-carboxamide	254.5	184.11	
60	2-ethyl-N-(phenyl(piperidin-4-yl)methyl)thiazole-5-carboxamide	330.3	149.92	
61	N-(4-(aminomethyl)phenyl)-2-ethylthiazole-5-carboxamide	261.9	113.72	
62	N-((1r,4r)-4-aminocyclohexyl)-3-cyclopropylbutanamide	225.6	155.29	
63	3-cyclopropyl-N-(phenyl(piperidin-4-yl)methyl)butanamide	301.3	131.22	
64	4-acetyl-N-((1r,4r)-4-aminocyclohexyl)-1H-pyrrole-2-carboxamide	250.2	134.14	

65	4-acetyl-N-(piperidin-4-yl)-1H-pyrrole-2-carboxamide	236	45.83	
66	4-acetyl-N-(4-(aminomethyl)phenyl)-1H-pyrrole-2-carboxamide	258.2	60.87	
67	N-((1r,4r)-4-aminocyclohexyl)-3-hydroxy-1-methyl-1H-pyrazole-5-carboxamide	238.8	129.1	
68	2-oxo-N-(piperidin-4-yl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carboxamide	261	86.06	
69	3-hydroxy-1-methyl-N-(piperidin-4-yl)-1H-pyrazole-5-carboxamide	225	19.72	
70	N-((1r,4r)-4-aminocyclohexyl)-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxamide	289	77.47	
71	N-((1r,4r)-4-aminocyclohexyl)-2-oxoindoline-6-carboxamide	274.2	89.26	
72	N-(1-(L-tyrosyl)piperidin-4-yl)-2-oxoindoline-6-carboxamide	423.5	35.48	
73	N-((1r,4r)-4-aminocyclohexyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxamide	275.1	13.7	
74	N-((1r,4r)-4-aminocyclohexyl)-2-oxo-1,2,3,4-tetrahydroquinoline-6-carboxamide	NA	65.8	
75	6-amino-N-((1r,4r)-4-aminocyclohexyl)-2-naphthamide	284.15	62.5	
76	N-((1r,4r)-4-aminocyclohexyl)-2-hydroxyquinoline-6-carboxamide	286.2	115.32	
77	N-(phenyl(piperidin-4-yl)methyl)-4-propionyl-1H-pyrrole-2-carboxamide	340.2	10.04	
78	N-((1r,4r)-4-aminocyclohexyl)-2-(ethylsulfonyl)propanamide	263.4	35.19	
79	N-((1r,4r)-4-aminocyclohexyl)-5-((dimethylamino)methyl)furan-2-carboxamide	266	38.86	
80	2-amino-N-(phenyl(piperidin-4-yl)methyl)oxazole-4-carboxamide	301.4	97.11	
81	N-(4-(aminomethyl)phenyl)-2-methyl-4H-furo[3,2-b]pyrrole-5-carboxamide	270.4	25.9	
82	N-(1-(L-tyrosyl)piperidin-4-yl)-1-methyl-2-oxoindoline-5-carboxamide	437.3	8.7	
83	N-(1-(L-tryptophyl)piperidin-4-yl)-1-methyl-2-oxoindoline-5-carboxamide	460.3	12.94	
84	N-((1r,4r)-4-aminocyclohexyl)-1-methyl-2-oxoindoline-5-carboxamide	288.2	16.66	
85	N-((1r,4r)-4-aminocyclohexyl)-8-methoxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide	NA	184.09	
86	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-oxoindoline-5-carboxamide	359.25	1.43	

87	N-(1-(1-(D-alanyl)piperidin-4-yl)ethyl)-2-oxoindoline-5-carboxamide	359.2	9.37	
88	N-(1-(L-tyrosyl)piperidin-4-yl)-1-methyl-2-oxoindoline-6-carboxamide		193.28	
89	N-((1r,4r)-4-aminocyclohexyl)-2-oxo-2,3-dihydrobenzo[d]oxazole-5-carboxamide	258.89 (-NH ₂)	140.17	
90	N-((1r,4r)-4-aminocyclohexyl)-2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxamide	276.15	9.76	
91	N-((1r,4r)-4-aminocyclohexyl)-2-oxo-1,2,3,4-tetrahydroquinoline-7-carboxamide	288.15	89.47	
92	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-7-carboxamide	373.2	49.95	
93	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxamide	360.25	6.76	
94	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxamide	361.25	3.94	
95	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-oxo-2H-chromene-6-carboxamide	372.3	149.61	
96	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-6-carboxamide	373.3	192.59	
97	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-6-amino-2-naphthamide	369.3	145.77	
98	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-8-methoxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide	405.25	150.97	
99	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-3-hydroxyquinoxaline-6-carboxamide	372.3	35.73	
100	2-oxo-N-(piperidin-4-ylmethyl)indoline-5-carboxamide	274.1	20.04	
101	(S)-2-oxo-N-(pyrrolidin-3-ylmethyl)indoline-5-carboxamide	260.1	25.36	
102	N-((1-(L-tyrosyl)piperidin-4-yl)methyl)-2-oxoindoline-5-carboxamide	437.45	1.86	
103	N-((1-(L-tryptophyl)piperidin-4-yl)methyl)-2-oxoindoline-5-carboxamide	460.25	2.74	
104	ethyl 2-(1-(L-alanyl)piperidin-4-yl)-2-(2-oxoindoline-5-carboxamido)acetate	417.3	1.51	
105	N-((4-hydroxypiperidin-4-yl)methyl)-2-oxoindoline-5-carboxamide	290.2	40.39	
106	N-(4-aminobutyl)-2-oxoindoline-5-carboxamide	248.2	13.42	
107	(S)-N-(4-(2-aminopropanamido)butyl)-2-oxoindoline-5-carboxamide	319.3	13.95	

108	ethyl 5-(((1r,4r)-4-aminocyclohexyl)amino)-5-oxopentanoate	257.3	92.19	
109	2-methyl-N-(phenyl(piperidin-4-yl)methyl)-3-(pyrrolidin-1-yl)propanamide	330.5	79.04	
110	2-methyl-N-(phenyl(piperidin-4-yl)methyl)-4H-furo[3,2-b]pyrrole-5-carboxamide	338.7	82.75	
111	N-((1r,4r)-4-aminocyclohexyl)-2-ethylpyrrolidine-2-carboxamide	240.1	149.59	
112	N-((1-(L-alanyl)-4-hydroxypiperidin-4-yl)methyl)-2-oxoindoline-5-carboxamide	361.15	3.04	
113	N-((1-(L-alanyl)-4-fluoropiperidin-4-yl)methyl)-2-oxoindoline-5-carboxamide	363.25	3.86	
114	(R)-N-(4-(2-aminopropanamido)butyl)-2-oxoindoline-5-carboxamide	319.15	22.28	
115	N-((1r,4r)-4-aminocyclohexyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-8-carboxamide	290	61.18	
116	N-((1r,4r)-4-aminocyclohexyl)-5-bromonicotinamide	296.13 / 298.13	51	
117	N-((1r,4r)-4-aminocyclohexyl)-5-chloronicotinamide	254.2	86.99	
118	N-((1r,4r)-4-aminocyclohexyl)benzo[d]thiazole-6-carboxamide	276.2	139.34	
119	N-((1r,4r)-4-aminocyclohexyl)-2-hydroxyquinoline-7-carboxamide		115.79	
120	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-hydroxyquinoline-7-carboxamide	371.2	86.89	
121	N-((4-methylpiperidin-4-yl)methyl)-2-oxoindoline-5-carboxamide	288.15	65.69	
122	ethyl 2-(2-oxoindoline-5-carboxamido)-2-(piperidin-4-yl)acetate	346.3	42.26	
123	6-amino-N-((1r,4r)-4-aminocyclohexyl)nicotinamide	235	107.83	
125	N-((1r,4r)-4-aminocyclohexyl)-7-fluoro-2-hydroxyquinoline-4-carboxamide	304.7	91.68	
126	N-((1r,4r)-4-aminocyclohexyl)-2-chloro-5-(4H-1,2,4-triazol-4-yl)benzamide	320.1	31.99	
127	N-((1r,4r)-4-aminocyclohexyl)-4H-1,2,4-triazole-3-carboxamide	210.1	16.44	
129	N-((1r,4r)-4-aminocyclohexyl)-2-(pyridin-3-yl)acetamide	234.1	> 100	
130	N-(4-(3-aminopropanamido)cyclohexyl)-2-oxoindoline-5-carboxamide	345.1	0.29	
131	ethyl 4-((2-oxoindoline-5-carboxamido)methyl)piperidine-4-carboxylate	346.2	56.28	

132	ethyl 1-(L-alanyl)-4-((2-oxoindoline-5-carboxamido)methyl)piperidine-4-carboxylate	417.2	0.94	
133	N-(((S)-1-(D-alanyl)pyrrolidin-3-yl)methyl)-2-oxoindoline-5-carboxamide	331.15	10.67	
134	N-(((S)-1-(L-alanyl)pyrrolidin-3-yl)methyl)-2-oxoindoline-5-carboxamide	331.15	10.2	
135	N-(((R)-1-(L-alanyl)pyrrolidin-3-yl)methyl)-2-oxoindoline-5-carboxamide	331.1	13.62	
136	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-4-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide	372.2	> 100	
137	N-((1r,4r)-4-aminocyclohexyl)-4-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide	301.1	46.61	
138	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)isonicotinamide	305.2	> 100	
139	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)isonicotinamide	291.2	> 100	
140	N-((1r,4r)-4-aminocyclohexyl)isonicotinamide	220.2	> 100	
141	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)nicotinamide	305.2	> 100	
142	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)nicotinamide	291.2	> 100	
143	N-((1r,4r)-4-aminocyclohexyl)nicotinamide	220.2	> 100	
144	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)pyrimidine-2-carboxamide	306.2	> 100	
145	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)pyrimidine-2-carboxamide	292.2	> 100	
146	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)benzo[d][1,3]dioxole-5-carboxamide	348.2	> 100	
147	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)benzo[d][1,3]dioxole-5-carboxamide	334.2	98.15	
148	N-((1r,4r)-4-aminocyclohexyl)benzo[d][1,3]dioxole-5-carboxamide	263.1	> 100	
149	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-3-(methylsulfonyl)benzamide	382.2	> 100	
150	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-3-(methylsulfonyl)benzamide	368.2	> 100	
151	N-((1r,4r)-4-aminocyclohexyl)-3-(methylsulfonyl)benzamide	297.1	> 100	

152	3-amino-N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)pyrazine-2-carboxamide	307.2	> 100	
153	3-amino-N-((1r,4r)-4-aminocyclohexyl)pyrazine-2-carboxamide	236.2	> 100	
154	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-[1,1'-biphenyl]-4-carboxamide	366.1	37.31	
155	N-((1r,4r)-4-aminocyclohexyl)-[1,1'-biphenyl]-4-carboxamide	295.1	79.21	
156	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-4-sulfamoylbenzamide	369.2	> 100	
157	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-5-fluoronicotinamide	323.2	> 100	
158	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-5-fluoronicotinamide	309.2	> 100	
159	N-((1r,4r)-4-aminocyclohexyl)-5-fluoronicotinamide	238.2	> 100	
160	N-((1r,4r)-4-aminocyclohexyl)-1H-indole-6-carboxamide	258.2	> 100	
161	N-((1r,4r)-4-aminocyclohexyl)-1H-benzo[d]imidazole-6-carboxamide	259.2	> 100	
162	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)quinoline-2-carboxamide	355.2	> 100	
163	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)quinoline-2-carboxamide	341.2	> 100	
164	N-((1r,4r)-4-aminocyclohexyl)quinoline-2-carboxamide	270.2	> 100	
165	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)isoquinoline-6-carboxamide	341.2	15.52	
166	N-((1r,4r)-4-aminocyclohexyl)isoquinoline-6-carboxamide	270.2	20.7	
167	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-(1H-indol-3-yl)acetamide	357.3	> 100	
168	N-((1r,4r)-4-aminocyclohexyl)-2-(1H-indol-3-yl)acetamide	272.2	> 100	
169	3-amino-N-((1r,4r)-4-(2-(6-methoxynaphthalen-2-yl)propanamido)cyclohexyl)propanamide	398.3	> 100	
170	N-((1r,4r)-4-aminocyclohexyl)-2-(6-methoxynaphthalen-2-yl)propanamide	327.3	76.38	
171	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)isoquinoline-1-carboxamide	355.3	> 100	

172	N-((1r,4r)-4-aminocyclohexyl)-1H-indazole-3-carboxamide	259	> 100	
173	N-((1r,4r)-4-(3-aminobutanamido)cyclohexyl)-2-oxoindoline-5-carboxamide	259.3	0.11	
174	N-((1r,4r)-4-(2-aminoacetamido)cyclohexyl)-2-oxoindoline-5-carboxamide	331.2	0.63	
175	N-((1r,4r)-4-(2-aminopropanamido)cyclohexyl)-2-oxoindoline-5-carboxamide	345.3	0.42	
176	N-((1-(L-alanyl)-4-methylpiperidin-4-yl)methyl)-2-oxoindoline-5-carboxamide	359.1	3.52	
177	N-(((R)-1-(D-alanyl)pyrrolidin-3-yl)methyl)-2-oxoindoline-5-carboxamide	331.15	19.78	
178	N-(4-(3-amino-N-methylpropanamido)cyclohexyl)-2-oxoindoline-5-carboxamide	359.3	3.4	
179	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide	386.2	> 100	
180	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-3,5-dimethyl-1H-pyrazole-4-carboxamide	322.3	> 100	
181	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-3,5-dimethyl-1H-pyrazole-4-carboxamide	308.2	> 100	
182	N-((1r,4r)-4-aminocyclohexyl)-3,5-dimethyl-1H-pyrazole-4-carboxamide	237.1	> 100	
183	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-methylpyrimidine-5-carboxamide	320.2	> 100	
184	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-2-methylpyrimidine-5-carboxamide	306.3	35.78	
185	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-5-methylpyrazine-2-carboxamide	320.3	> 100	
186	N-((1r,4r)-4-aminocyclohexyl)-5-methylpyrazine-2-carboxamide	235.2	> 100	
187	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-aminoisonicotinamide	320.3	> 100	
188	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-3-aminopyrazine-2-carboxamide	321.2	> 100	
189	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-[1,1'-biphenyl]-4-carboxamide	380.3	> 100	
190	N-((1r,4r)-4-aminocyclohexyl)-4-sulfamoylbenzamide	298.2	> 100	
191	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-6-hydroxypyridazine-3-carboxamide	322.2	> 100	
192	N-((1r,4r)-4-aminocyclohexyl)-1H-indole-5-carboxamide	258.2	> 100	

193	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-1H-benzo[d]imidazole-6-carboxamide	344.3	> 100	
194	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)isoquinoline-6-carboxamide	355.2	> 100	
195	N-((1r,4r)-4-(2-(1H-indol-3-yl)acetamido)cyclohexyl)-3-aminopropanamide	343.2	> 100	
196	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)isoquinoline-1-carboxamide	341.2	> 100	
197	N-((1r,4r)-4-aminocyclohexyl)isoquinoline-1-carboxamide	270.2	> 100	
198	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-5-fluoro-1H-indole-2-carboxamide	361.2	41.66	
199	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-hydroxyquinoline-4-carboxamide	371.3	> 100	
200	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-2-hydroxyquinoline-4-carboxamide	357.2	23.31	
201	N-((1r,4r)-4-aminocyclohexyl)-2-hydroxyquinoline-4-carboxamide	286.2	> 100	
202	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxamide	358.3	59	
203	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-5,6,7,8-tetrahydronaphthalene-2-carboxamide	344.2	11.21	
204	N-((1r,4r)-4-aminocyclohexyl)-5,6,7,8-tetrahydronaphthalene-2-carboxamide	273.2	47.43	
205	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)pyrazine-2-carboxamide	306.3	> 100	
206	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-(4-fluorophenyl)acetamide	336.2	> 100	
207	3-amino-N-((1r,4r)-4-(2-(4-fluorophenyl)acetamido)cyclohexyl)propanamide	322.2	> 100	
208	N-((1r,4r)-4-aminocyclohexyl)-2-(4-fluorophenyl)acetamide	251.2	> 100	
209	4-((1-(1-(L-alanyl)piperidin-4-yl)ethyl)carbamoyl)pyridine 1-oxide	321.2	> 100	
210	4-(((1r,4r)-4-aminocyclohexyl)carbamoyl)pyridine 1-oxide	236.2	> 100	
211	4-amino-N-((1r,4r)-4-aminocyclohexyl)quinoline-6-carboxamide	285.15	43.73	
212	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-aminoquinoline-6-carboxamide	370.3	15.16	
213	(R)-2-oxo-N-(pyrrolidin-3-ylmethyl)indoline-5-carboxamide	260.15	17.95	

214	N-(4-(2-amino-N-methylacetamido)cyclohexyl)-2-oxoindoline-5-carboxamide	345.3	1.25	
215	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-5-methylpyrazine-2-carboxamide	306.1	> 100	
216	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-(4-bromo-3,5-dimethyl-1H-pyrazol-1-yl)propanamide	428.2	> 100	
217	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carboxamide	385.3	> 100	
218	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide	400.3	76.96	
219	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-1-methyl-1H-indazole-6-carboxamide	358.2	> 100	
220	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-6-methoxy-2-naphthamide	384.2	> 100	
221	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-methoxyquinoline-4-carboxamide	385.1	> 100	
222	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-2-methoxyquinoline-4-carboxamide	371	> 100	
223	N-((1r,4r)-4-aminocyclohexyl)-2-methoxyquinoline-4-carboxamide	300	> 100	
224	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-oxo-4H-chromene-2-carboxamide	372.2	> 100	
225	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-hydroxyquinoline-2-carboxamide	371.2	> 100	
226	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-(4H-1,2,4-triazol-4-yl)benzamide	371.2	> 100	
227	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-(pyrrolidin-1-yl)benzamide	373.3	29.17	
228	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)benzo[d]thiazole-6-carboxamide	361.2	> 100	
229	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-5-chloro-1H-indole-2-carboxamide	377.2	77.9	
230	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-5-chloro-1H-indole-2-carboxamide	363.1	37.47	
231	N-((1r,4r)-4-aminocyclohexyl)-5-chloro-1H-indole-2-carboxamide	292.1	91.53	
232	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-1H-indole-2-carboxamide	343.3	> 100	
233	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-1H-indole-2-carboxamide	329.3	> 100	

234	N-((1r,4r)-4-aminocyclohexyl)-1H-indole-2-carboxamide	258.2	> 100	
235	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-1H-indole-5-carboxamide	329.2	13.44	
236	5-((1-(1-(L-alanyl)piperidin-4-yl)ethyl)carbamoyl)benzo[c][1,2,5]oxadiazole 1-oxide	362.2	> 100	
237	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)benzo[c][1,2,5]oxadiazole-5-carboxamide	346.2	> 100	
238	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)quinoxaline-2-carboxamide	356.3	> 100	
239	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)imidazo[2,1-b]thiazole-6-carboxamide	350.2	> 100	
241	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-(1H-imidazol-1-yl)butanamide	336.3	82.88	
242	N-((1r,4r)-4-aminocyclohexyl)-5-fluoro-1H-indole-2-carboxamide	276	> 100	
243	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-1H-benzo[d]imidazole-2-carboxamide	344.2	72.93	
244	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-1-methyl-1H-indole-2-carboxamide	357.2	> 100	
245	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-1-methyl-1H-indole-2-carboxamide	343.3	> 100	
246	N-((1r,4r)-4-aminocyclohexyl)-1-methyl-1H-indole-2-carboxamide	272.2	> 100	
247	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-aminonicotinamide	320.2	> 100	
248	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-1H-indole-4-carboxamide	343.3	> 100	
249	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-hydroxyisonicotinamide	321.2	65.86	
250	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-hydroxyisonicotinamide	321.2	> 100	
251	N-((1r,4r)-4-aminocyclohexyl)picolinamide	220.1	> 100	
252	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)pyrazine-2-carboxamide	292.1	37.36	
253	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-1-methyl-1H-imidazole-2-carboxamide	308.2	64.91	
254	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-3-methylisonicotinamide	319.3	> 100	
255	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-methylnicotinamide	319.3	73.38	

256	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-5-methylnicotinamide	319.3	61.59	
257	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-6-methylnicotinamide	319.3	> 100	
258	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-3-methylisothiazole-4-carboxamide	325.3	> 100	
259	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-1-methyl-1H-pyrazole-3-carboxamide	308.3	> 100	
260	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-3-(tert-butyl)-1-methyl-1H-pyrazole-5-carboxamide	364.3	> 100	
261	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-6-methoxypyrazine-2-carboxamide	336.2	> 100	
262	(1r,4S)-N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-aminocyclohexane-1-carboxamide	325.2	> 100	
263	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-chloro-2-(trifluoromethyl)benzamide	406.2	> 100	
264	4-(((1r,4r)-4-(3-aminopropanamido)cyclohexyl)carbamoyl)pyridine 1-oxide	307.2	> 100	
265	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-6-fluoropicolinamide	323.2	> 100	
266	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2,2-difluorobenzo[d][1,3]dioxole-4-carboxamide	384.3	> 100	
267	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-3-fluoroisonicotinamide	323.2	> 100	
268	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide	343.3	> 100	
269	N-((1r,4r)-4-aminocyclohexyl)pyrimidine-2-carboxamide	221.1	> 100	
270	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-6-hydroxypyridazine-3-carboxamide	308.2	> 100	
271	N-((1r,4r)-4-aminocyclohexyl)-6-hydroxypyridazine-3-carboxamide	237.2	> 100	
272	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-1H-indole-6-carboxamide	329.2	37.25	
273	N-((1r,4r)-4-aminocyclohexyl)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carboxamide	300.1	> 100	
274	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide	349.3	> 100	
275	N-((1r,4r)-4-aminocyclohexyl)-1-methyl-1H-indazole-6-carboxamide	273	> 100	
276	N-((1r,4r)-4-aminocyclohexyl)-6-methoxy-2-naphthamide	299.1	> 100	

277	N-((1r,4r)-4-aminocyclohexyl)-4-oxo-4H-chromene-2-carboxamide	287	> 100	
278	N-((1r,4r)-4-aminocyclohexyl)-4-(4H-1,2,4-triazol-4-yl)benzamide	286	> 100	
279	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-4-(pyrrolidin-1-yl)benzamide	359.1	43.65	
280	N-((1r,4r)-4-aminocyclohexyl)-4-(pyrrolidin-1-yl)benzamide	288.1	48.03	
281	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)benzo[d]thiazole-6-carboxamide	347	28.96	
283	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-1H-indole-5-carboxamide	343.2	> 100	
284	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide	384.2	> 100	
285	N-((1r,4r)-4-aminocyclohexyl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide	299.2	69.12	
286	5-(((1r,4r)-4-aminocyclohexyl)carbamoyl)benzo[c][1,2,5]oxadiazole 1-oxide	277.1	> 100	
287	N-((1r,4r)-4-aminocyclohexyl)benzo[c][1,2,5]oxadiazole-5-carboxamide	261	> 100	
288	4-amino-N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)nicotinamide	306.1	> 100	
289	4-amino-N-((1r,4r)-4-aminocyclohexyl)nicotinamide	235.2	> 100	
290	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-1H-indole-4-carboxamide	329.2	> 100	
291	N-((1r,4r)-4-aminocyclohexyl)-1H-indole-4-carboxamide	258.2	> 100	
292	N-((1r,4r)-4-aminocyclohexyl)-2-hydroxyisonicotinamide	236.2	> 100	
293	N-((1r,4r)-4-aminocyclohexyl)-2-hydroxyisonicotinamide	236.1	> 100	
294	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-6-hydroxynicotinamide	307.2	> 100	
295	N-((1r,4r)-4-aminocyclohexyl)-6-hydroxynicotinamide	236.2	> 100	
296	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)picolinamide	305.2	> 100	
297	N-(4-(3-aminopropanamido)cyclohexyl)picolinamide	291.2	44.24	
298	N-((1r,4r)-4-aminocyclohexyl)pyrazine-2-carboxamide	221.2	> 100	

299	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-3-(tert-butyl)-1-(3-methylbenzyl)-1H-pyrazole-5-carboxamide	454.3	> 100	
300	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-7-methyl-1H-indole-2-carboxamide	357.2	> 100	
301	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-6-methoxypicolinamide	335.2	> 100	
302	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-5-methoxypyrazine-2-carboxamide	336.2	> 100	
303	(1r,4r)-4-amino-N-(((1r,4r)-4-(3-aminopropanamido)cyclohexyl)cyclohexane-1-carboxamide	311.2	> 100	
304	(1r,4r)-4-amino-N-(((1r,4r)-4-aminocyclohexyl)cyclohexane-1-carboxamide	240.1	> 100	
305	(2S,4S)-N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-fluoropyrrolidine-2-carboxamide	315.2	55.92	
306	(3R)-N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	359.3	48.06	
307	N-(((1r,4r)-4-aminocyclohexyl)-2,2-difluorobenzo[d][1,3]dioxole-4-carboxamide	299	> 100	
308	N-(((1r,4r)-4-aminocyclohexyl)-3-fluoroisonicotinamide	238.2	> 100	
309	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)thiazole-5-carboxamide	311.2	> 100	
310	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-5-hydroxypicolinamide	321.2	> 100	
311	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxamide	324.2	> 100	
312	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-1H-indazole-3-carboxamide	344.2	> 100	
313	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-(3,5-difluorophenyl)acetamide	354.2	70.71	
314	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-(pyridin-3-yl)acetamide	319.2	> 100	
315	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-(pyrimidin-5-yl)acetamide	320.3	> 100	
316	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-(1H-imidazol-1-yl)acetamide	308.2	> 100	
317	N-(((1r,4r)-4-(3-aminopropanamido)cyclohexyl)imidazo[2,1-b]thiazole-6-carboxamide	336	> 100	
318	N-(((1r,4r)-4-aminocyclohexyl)imidazo[2,1-b]thiazole-6-carboxamide	265	> 100	
319	N-(((1r,4r)-4-aminocyclohexyl)imidazo[2,1-b]thiazole-6-carboxamide	265.2	> 100	

320	N-((1r,4r)-4-aminocyclohexyl)-2-methylpyrimidine-5-carboxamide	235.1	> 100	
321	2-amino-N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)isonicotinamide	306.2	16.59	
322	2-amino-N-((1r,4r)-4-aminocyclohexyl)isonicotinamide	235.1	> 100	
323	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-sulfamoylbenzamide	383	> 100	
324	N-((1r,4r)-4-aminocyclohexyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide	264.1	> 100	
325	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-1-methyl-1H-indazole-6-carboxamide	344.3	> 100	
326	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-6-methoxy-2-naphthamide	370.3	28	
327	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-4-oxo-4H-chromene-2-carboxamide	358.2	> 100	
328	N-((1r,4r)-4-aminocyclohexyl)-4-hydroxyquinoline-2-carboxamide	286.2	> 100	
329	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-4-(4H-1,2,4-triazol-4-yl)benzamide	357.3	> 100	
330	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide	370.2	7.49	
331	5-(((1r,4r)-4-(3-aminopropanamido)cyclohexyl)carbamoyl)benzo[c][1,2,5]oxadiazole 1-oxide	348.2	85.12	
332	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)benzo[c][1,2,5]oxadiazole-5-carboxamide	332.2	> 100	
333	N-((1r,4r)-4-aminocyclohexyl)-4-(1H-imidazol-1-yl)butanamide	251.1	> 100	
334	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-(6-methoxynaphthalen-2-yl)propanamide	412.3	34.86	
335	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-5-fluoro-1H-indole-2-carboxamide	347.2	> 100	
336	N-((1r,4r)-4-aminocyclohexyl)-1H-benzo[d]imidazole-2-carboxamide	259.1	> 100	
337	N-((1r,4r)-4-aminocyclohexyl)-1-methyl-1H-imidazole-2-carboxamide	223.1	> 100	
338	(1r,4r)-N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide	320.3	> 100	

339	N-((1r,4r)-4-aminocyclohexyl)-4-methylnicotinamide	234.1	> 100	
340	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-3-(tert-butyl)-1-(3-methylbenzyl)-1H-pyrazole-5-carboxamide	440.3	> 100	
341	N-((1r,4r)-4-aminocyclohexyl)-3-(tert-butyl)-1-(3-methylbenzyl)-1H-pyrazole-5-carboxamide	369.1	> 100	
342	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-7-methyl-1H-indole-2-carboxamide	343.2	37.68	
343	N-((1r,4r)-4-aminocyclohexyl)-7-methyl-1H-indole-2-carboxamide	272.2	68.49	
344	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-5-methylnicotinamide	305.1	36.4	
345	N-((1r,4r)-4-aminocyclohexyl)-5-methylnicotinamide	234.2	50.67	
346	N-((1r,4r)-4-aminocyclohexyl)-6-methylnicotinamide	234.1	> 100	
347	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-3-methylisothiazole-4-carboxamide	311.2	> 100	
348	N-((1r,4r)-4-aminocyclohexyl)-3-methylisothiazole-4-carboxamide	240.2	> 100	
349	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-1-methyl-1H-pyrazole-3-carboxamide	294.2	> 100	
350	N-((1r,4r)-4-aminocyclohexyl)-1-methyl-1H-pyrazole-3-carboxamide	223.2	> 100	
351	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-3-(tert-butyl)-1-methyl-1H-pyrazole-5-carboxamide	350.3	> 100	
352	N-((1r,4r)-4-aminocyclohexyl)-3-(tert-butyl)-1-methyl-1H-pyrazole-5-carboxamide	279.3	> 100	
353	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-6-methoxypicolinamide	321.2	> 100	
354	N-((1r,4r)-4-aminocyclohexyl)-6-methoxypicolinamide	250.2	> 100	
355	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-6-methoxypyrazine-2-carboxamide	322	> 100	
356	N-((1r,4r)-4-aminocyclohexyl)-6-methoxypyrazine-2-carboxamide	251.2	> 100	
357	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-5-aminopicolinamide	320.2	> 100	

358	N-((1r,4r)-4-aminocyclohexyl)-4-chloro-2-(trifluoromethyl)benzamide	320.9	> 100	
359	N-((1r,4r)-4-aminocyclohexyl)thiazole-5-carboxamide	226.1	> 100	
360	N-((1r,4r)-4-aminocyclohexyl)-1H-indole-3-carboxamide	258.1	> 100	
361	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-5-hydroxypicolinamide	307.1	> 100	
362	N-((1r,4r)-4-aminocyclohexyl)-2-(3,5-difluorophenyl)acetamide	269.2	> 100	
363	3-amino-N-((1r,4r)-4-(2-(pyridin-3-yl)acetamido)cyclohexyl)propanamide	305.1	> 100	
364	3-amino-N-((1r,4r)-4-(2-(pyrimidin-5-yl)acetamido)cyclohexyl)propanamide	306.2	> 100	
365	N-((1r,4r)-4-aminocyclohexyl)-2-(pyrimidin-5-yl)acetamide	235.2	> 100	
366	N-((1r,4r)-4-(2-(1H-imidazol-1-yl)acetamido)cyclohexyl)-3-aminopropanamide	294.1	> 100	
367	N-((1r,4r)-4-aminocyclohexyl)benzo[d]thiazole-2-carboxamide	276.1	> 100	
368	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-1H-indole-6-carboxamide	343.3	12.33	
369	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-1H-benzo[d]imidazole-5-carboxamide	330.1	65.22	
370	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-methoxy-1H-indole-3-carboxamide	373.2	> 100	
371	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-4-methoxy-1H-indole-3-carboxamide	359.2	> 100	
372	N-((1r,4r)-4-aminocyclohexyl)-4-methoxy-1H-indole-3-carboxamide	288.1	> 100	
373	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)quinoxaline-2-carboxamide	342.1	> 100	
374	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-1H-benzo[d]imidazole-2-carboxamide	330.3	86.56	
375	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-4-(1H-imidazol-1-yl)butanamide	322.2	> 100	
376	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-2-hydroxyisonicotinamide	307.2	> 100	

378	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-6-hydroxynicotinamide	321.1	> 100	
379	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-3-methylisonicotinamide	305.1	> 100	
380	N-((1r,4r)-4-aminocyclohexyl)-3-methylisonicotinamide	234.1	> 100	
381	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-4-methylnicotinamide	305.1	> 100	
382	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-6-methylnicotinamide	305.2	> 100	
383	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-5-methoxypyrazine-2-carboxamide	322.1	> 100	
384	N-((1r,4r)-4-aminocyclohexyl)-5-methoxypyrazine-2-carboxamide	251	> 100	
385	6-amino-N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)picolinamide	306.2	> 100	
386	6-amino-N-((1r,4r)-4-aminocyclohexyl)picolinamide	235.1	> 100	
387	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-6-aminonicotinamide	320.2	> 100	
388	6-amino-N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)nicotinamide	306.2	> 100	
389	N-((1r,4r)-4-aminocyclohexyl)-6-fluoropicolinamide	238.2	> 100	
390	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-3-fluoroisonicotinamide	309.2	> 100	
391	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-1H-indole-3-carboxamide	329.1	> 100	
392	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-methylisonicotinamide	319.2	> 100	
393	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-2-methylisonicotinamide	305.2	> 100	
394	N-((1r,4r)-4-aminocyclohexyl)-2-methylisonicotinamide	234.1	> 100	
395	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)benzo[d]thiazole-2-carboxamide	361.2	> 100	
396	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-5-methylthiazole-2-carboxamide	325	10.61	
397	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-5-methylthiazole-2-carboxamide	311	27.42	

398	N-((1r,4r)-4-aminocyclohexyl)-5-methylthiazole-2-carboxamide	240.1	> 100	
399	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-oxoindoline-4-carboxamide	359.2	> 100	
400	N-((1r,4r)-4-aminocyclohexyl)-2-oxoindoline-4-carboxamide	274.2	> 100	
401	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carboxamide	371.1	> 100	
402	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide	335.2	> 100	
403	N-((1r,4r)-4-aminocyclohexyl)-4-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide	315.1	> 100	
404	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-4-hydroxyquinoline-2-carboxamide	357.2	> 100	
405	N-((1r,4r)-4-aminocyclohexyl)quinoxaline-2-carboxamide	271.2	> 100	
406	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-(1H-pyrrolo[3,2-b]pyridin-3-yl)acetamide	358.2	> 100	
407	N-((1r,4r)-4-(2-(1H-pyrrolo[3,2-b]pyridin-3-yl)acetamido)cyclohexyl)-3-aminopropanamide	344.2	> 100	
408	N-((1r,4r)-4-aminocyclohexyl)-2-(1H-pyrrolo[3,2-b]pyridin-3-yl)acetamide	273.2	> 100	
409	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-hydroxynicotinamide	321.2	70.41	
410	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-2-hydroxynicotinamide	307.3	44.48	
411	N-((1r,4r)-4-aminocyclohexyl)-2-hydroxynicotinamide	236.2	> 100	
412	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-1-methyl-1H-imidazole-2-carboxamide	294.1	> 100	
413	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-1-methyl-1H-pyrazole-5-carboxamide	308.1	> 100	
414	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-1-methyl-1H-pyrazole-5-carboxamide	294.1	> 100	
415	N-((1r,4r)-4-aminocyclohexyl)-1-methyl-1H-pyrazole-5-carboxamide	223.1	> 100	
416	(1R,4R)-N-((1r,4R)-4-(3-aminopropanamido)cyclohexyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide	306.1	> 100	

417	(1r,4r)-N-((1r,4R)-4-aminocyclohexyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide	235.1	> 100	
418	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-6-aminopicolinamide	320.3	> 100	
419	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-aminopyrimidine-5-carboxamide	321.2	> 100	
420	4-amino-N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)pyrimidine-5-carboxamide	307.2	> 100	
421	4-amino-N-((1r,4r)-4-aminocyclohexyl)pyrimidine-5-carboxamide	236.1	> 100	
422	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-6-fluoropicolinamide	309.2	> 100	
423	N-((1r,4r)-4-aminocyclohexyl)-5-hydroxypicolinamide	236.2	> 100	
424	N-((1r,4r)-4-aminocyclohexyl)-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxamide	239.1	> 100	
425	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-1H-indazole-3-carboxamide	330.1	37.49	
426	N-((1r,4r)-4-aminocyclohexyl)-2-(1H-imidazol-1-yl)acetamide	223.1	> 100	
427	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)benzo[d]thiazole-2-carboxamide	347.2	> 100	
428	(1r,4r)-4-amino-N-(2-oxoindolin-5-yl)cyclohexane-1-carboxamide	274.1	30.6	
429	N-((1r,4r)-4-aminocyclohexyl)-2-oxoindoline-5-sulfonamide	310	14.5	
430	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-2-oxoindoline-4-carboxamide	345.2	> 100	
431	3-amino-N-((1r,4r)-4-(2-(4-bromo-3,5-dimethyl-1H-pyrazol-1-yl)propanamido)cyclohexyl)propanamide		> 100	
432	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-4-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide	386.3	36.97	
433	(2R,4S)-N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-hydroxypyrrolidine-2-carboxamide	313.2	45.65	
434	(2R,4S)-N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-4-hydroxypyrrolidine-2-carboxamide	299.2	> 100	

435	(2R,4S)-N-((1r,4r)-4-aminocyclohexyl)-4-hydroxypyrrolidine-2-carboxamide	228.1	> 100	
436	(R)-N-((1r,4r)-4-aminocyclohexyl)-1,2,3,4-tetrahydroquinoline-2-carboxamide	274.1	12.51	
437	5-amino-N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)picolinamide	306.2	> 100	
438	5-amino-N-((1r,4r)-4-aminocyclohexyl)picolinamide	235.2	> 100	
439	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-4-chloro-2-(trifluoromethyl)benzamide	392.2	> 100	
440	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-2,2-difluorobenzo[d][1,3]dioxole-4-carboxamide	370.2	> 100	
441	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-3,5-dihydroxy-2-naphthamide	386.1	37.45	
442	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)thiazole-5-carboxamide	297.2	> 100	
443	3-amino-N-((1r,4r)-4-(2-(3,5-difluorophenyl)acetamido)cyclohexyl)propanamide	340.2	> 100	
444	5-acetamido-N-((1r,4r)-4-aminocyclohexyl)picolinamide	277	> 100	
445	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)imidazo[1,2-b]pyridazine-2-carboxamide	345	> 100	
446	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)imidazo[1,2-b]pyridazine-2-carboxamide	331.1	> 100	
447	N-((1r,4r)-4-aminocyclohexyl)imidazo[1,2-b]pyridazine-2-carboxamide	260	> 100	
448	N-((1r,4r)-4-aminocyclohexyl)-2-(2-oxoindolin-5-yl)acetamide	288.2	> 100	
449	3-amino-N-((1r,4r)-4-((2-oxoindoline)-5-sulfonamido)cyclohexyl)propanamide	381.1	> 100	
450	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide	389.2	25.37	
451	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide	375.2	9.9	
452	N-((1r,4r)-4-aminocyclohexyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide	304.2	39.15	

453	N-((1R,4r)-4-((R)-3-aminobutanamido)cyclohexyl)-2-oxoindoline-5-carboxamide	359.2	0.26	> 40
454	N-((1r,4r)-4-aminocyclohexyl)-2-(4-bromo-3,5-dimethyl-1H-pyrazol-1-yl)propanamide	342.9	> 100	
455	N-((1r,4r)-4-aminocyclohexyl)-4-(1H-1,2,4-triazol-1-yl)benzamide	286.2	> 100	
456	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-2-hydroxyquinoline-3-carboxamide	357.2	21.97	
457	N-((1r,4r)-4-aminocyclohexyl)-2-(3-(trifluoromethyl)phenyl)acetamide	301	> 100	
458	3-amino-N-((1r,4r)-4-aminocyclohexyl)-2-methylquinoline-4-carboxamide	299.1	> 100	
459	(3R)-N-(4-aminocyclohexyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	274.1	> 100	
460	N-((1r,4r)-4-aminocyclohexyl)-3,5-dihydroxy-2-naphthamide	301	20.71	
461	5-(2-(piperidin-4-yl)acetyl)octahydro-2H-pyrrolo[3,2-c]pyridin-2-one	266.1	> 100	
462	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-5-acetamidopicolinamide	362.1	> 100	
463	5-acetamido-N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)picolinamide	348	> 100	
464	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-5-cyclopropyl-1,2,4-oxadiazole-3-carboxamide	336.2	32.68	
465	3-amino-N-((1r,4r)-4-(2-(2-oxoindolin-5-yl)acetamido)cyclohexyl)propanamide	359.2	38.81	
466	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-(2-oxoindolin-5-yl)acetamide	373.2	60	
467	(1r,4r)-4-(3-aminopropanamido)-N-(2-oxoindolin-5-yl)cyclohexane-1-carboxamide	345	4.46	
468	3-amino-N-(2,2-dimethyl-3-((2-oxoindoline)-5-sulfonamido)propyl)propanamide	369.2	18.32	
469	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-1-oxoisoindoline-5-carboxamide	359.2	> 100	
470	N-((1r,4r)-4-aminocyclohexyl)-2,3-dioxoindoline-5-carboxamide	288	7.46	
471	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-2-oxoindoline-5-carboxamide	345.2	0.61	
472	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-(1H-1,2,4-triazol-1-yl)benzamide	371.3	> 100	
473	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-4-(1H-1,2,4-triazol-1-yl)benzamide	357.2	53.11	
474	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-hydroxyquinoline-3-carboxamide	371.2	22.09	

475	N-((1r,4r)-4-aminocyclohexyl)-2-hydroxyquinoline-3-carboxamide	286.2	22.16	
476	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-(3-(trifluoromethyl)phenyl)acetamide	386.1	51.13	
477	3-amino-N-((1r,4r)-4-(2-(3-(trifluoromethyl)phenyl)acetamido)cyclohexyl)propanamide	372	22.78	
478	3-amino-N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-2-methylquinoline-4-carboxamide	370.2	31.62	
479	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-3,5-dihydroxy-2-naphthamide	372	5.02	
480	N-((1r,4r)-4-aminocyclohexyl)-3-hydroxypicolinamide	236.2	> 100	
481	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxamide	310.2	15.1	
482	(E)-N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-3-(1H-imidazol-4-yl)acrylamide	306.1	71.06	
483	5-(2-(1-(3-aminopropanoyl)piperidin-4-yl)acetyl)octahydro-2H-pyrrolo[3,2-c]pyridin-2-one	337.2	10.25	
484	N-((1r,4r)-4-aminocyclohexyl)-5-cyclopropyl-1,2,4-oxadiazole-3-carboxamide	251.1	85.66	
485	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-5-cyclopropyl-1,2,4-oxadiazole-3-carboxamide	322.1	12.92	
486	2-amino-N-(2,2-dimethyl-3-((2-oxoindoline)-5-sulfonamido)propyl)acetamide	355	18.82	
487	N-((1r,4r)-4-aminocyclohexyl)-1-oxoisoindoline-5-carboxamide	274.1	37.89	
488	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2,3-dioxoindoline-5-carboxamide	373.1	14.08	
489	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-3-amino-2-methylquinoline-4-carboxamide	384.3	31.62	
490	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-6-chloro-2-oxoindoline-5-carboxamide	393.2	0.43	> 40
491	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-6-chloro-2-oxoindoline-5-carboxamide	379.2	0.15	> 40
492	N-((1r,4r)-4-aminocyclohexyl)-6-chloro-2-oxoindoline-5-carboxamide	308.1	1.59	
493	N-((1r,4r)-4-aminocyclohexyl)-4-hydroxypyrimidine-5-carboxamide	237.1	> 50	
494	(E)-N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-3-(1H-imidazol-4-yl)acrylamide	320.2	> 100	

495	(E)-N-((1r,4r)-4-aminocyclohexyl)-3-(1H-imidazol-4-yl)acrylamide	235.1	> 100	
496	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-1H-pyrazolo[3,4-c]pyridine-5-carboxamide	345.2	6.57	
497	N-((1r,4r)-4-aminocyclohexyl)-1H-pyrazolo[3,4-c]pyridine-5-carboxamide	260	35.73	
498	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-6-fluorobenzo[d]thiazole-2-carboxamide	379	51	
499	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-6-fluorobenzo[d]thiazole-2-carboxamide	365.2	86.27	
500	N-((1r,4r)-4-aminocyclohexyl)-6-fluorobenzo[d]thiazole-2-carboxamide	294.1	> 100	
501	1-(2-amino-2-oxoethyl)-N-((1r,4r)-4-aminocyclohexyl)-1H-1,2,3-triazole-4-carboxamide	267.2	50	
502	N-((1r,4r)-4-aminocyclohexyl)-1H-imidazole-2-carboxamide	209.1	> 100	
503	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-1-oxoisoindoline-5-carboxamide	345.2	> 100	
504	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-2,3-dioxoindoline-5-carboxamide	359	5.38	
505	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-2-oxoindoline-7-carboxamide	345.2	16.1	
506	N-(4-aminocyclohexyl)-2-oxoindoline-7-carboxamide	274.2	42.25	
507	N-((1r,4r)-4-aminocyclohexyl)-1-methyl-1H-1,2,4-triazole-5-carboxamide	224.2	> 100	
508	3-amino-N-((1r,4r)-4-aminocyclohexyl)-1H-1,2,4-triazole-5-carboxamide	225	> 50	
509	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4-hydroxypyrimidine-5-carboxamide	322.1	> 50	
510	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-4-hydroxypyrimidine-5-carboxamide	308.1	> 50	
511	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-3-hydroxypicolinamide	321.1	> 50	
512	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-3-hydroxypicolinamide	307	> 50	
513	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-5-hydroxynicotinamide	321.2	> 50	
514	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-5-hydroxynicotinamide	307.1	> 50	

515	N-((1r,4r)-4-aminocyclohexyl)-5-hydroxynicotinamide	236.1	> 50	
516	1-(2-amino-2-oxoethyl)-N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-1H-1,2,3-triazole-4-carboxamide	338.2	> 50	
517	N-(4-aminocyclohexyl)-1H-imidazole-4-carboxamide	209.2	> 50	
518	N-(4-(3-aminopropanamido)cyclohexyl)-1H-imidazole-2-carboxamide	280.2	> 50	
519	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-2-methyl-1H-indole-5-carboxamide	343.2	> 50	
520	N-((1r,4r)-4-aminocyclohexyl)-2-methyl-1H-indole-5-carboxamide	272.2	> 50	
521	N-((1r,4r)-4-aminocyclohexyl)-1H-imidazole-4-carboxamide	209.2	> 50	
522	N-((1r,4r)-4-aminocyclohexyl)-2-methyl-1H-imidazole-5-carboxamide	223.2	> 50	
523	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-4H-1,2,4-triazole-3-carboxamide	295.1	> 50	
525	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-4H-1,2,4-triazole-3-carboxamide	281.1	> 50	
527	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-5-chloro-1H-pyrazole-3-carboxamide	328	> 50	
528	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-5-chloro-1H-pyrazole-3-carboxamide	314	> 50	
529	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-1H-pyrazolo[3,4-c]pyridine-5-carboxamide	331.2	4.45	
530	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-carboxamide	297.1	> 50	
531	N-((1r,4r)-4-aminocyclohexyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-carboxamide	226.1	> 50	
532	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)thiazolo[5,4-c]pyridine-2-carboxamide	348.1	> 50	
533	N-((1r,4r)-4-aminocyclohexyl)thiazolo[5,4-c]pyridine-2-carboxamide	277.1	> 50	
534	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-1-(2-amino-2-oxoethyl)-1H-1,2,3-triazole-4-carboxamide	352.2	> 50	
535	N-((1r,4r)-4-aminocyclohexyl)-5-ethyl-1H-1,2,4-triazole-3-carboxamide	238.1	> 50	

536	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-5-ethyl-4H-1,2,4-triazole-3-carboxamide	309.2	> 50	
537	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-1H-imidazole-4-carboxamide	280.2	> 50	
538	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-2-methyl-1H-indole-5-carboxamide	357.2	> 50	
539	N-((1R,4r)-4-((1r,4R)-4-aminocyclohexane-1-carboxamido)cyclohexyl)-1H-1,2,4-triazole-5-carboxamide	335.2	> 50	
540	N-((1r,4r)-4-(4-aminobutanamido)cyclohexyl)-4H-1,2,4-triazole-3-carboxamide	295.1	> 50	
541	N-((1r,4r)-4-aminocyclohexyl)-5-chloro-1H-1,2,4-triazole-3-carboxamide	244.1	> 50	
542	N-((1r,4r)-4-aminocyclohexyl)-5-methyl-1H-imidazole-4-carboxamide	223.1	> 50	
543	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-5-methyl-4H-1,2,4-triazole-3-carboxamide	295.1	> 50	
544	N-((1r,4r)-4-aminocyclohexyl)-1-methyl-1H-1,2,4-triazole-3-carboxamide	224.2	> 50	
545	N-((1r,4r)-4-aminocyclohexyl)-5-chloro-1H-pyrazole-3-carboxamide	243.1	> 50	
546	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-carboxamide	311.1	9.76	
547	N-(1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)-4H-1,2,4-triazole-3-carboxamide	321.2	> 50	
548	N-((1r,4r)-4-aminocyclohexyl)-3-iodo-1H-1,2,4-triazole-5-carboxamide	335.9	> 50	
549	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-3-methyl-1H-1,2,4-triazole-5-carboxamide	309.2	> 50	
550	N-((1r,4r)-4-aminocyclohexyl)-5-methyl-1H-1,2,4-triazole-3-carboxamide	224.1	14.71	
551	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)thiazolo[5,4-c]pyridine-2-carboxamide	362.2	> 50	
552	N-(1-(1-(L-alanyl)piperidin-4-yl)ethyl)-5-ethylthiazole-2-carboxamide	339.2	6.44	
553	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-5-ethylthiazole-2-carboxamide	325.2	25.61	
554	N-((1r,4r)-4-aminocyclohexyl)-5-ethylthiazole-2-carboxamide	254.1	> 50	

555	N-(1-((1r,4r)-4-aminocyclohexane-1-carbonyl)piperidin-4-yl)-4H-1,2,4-triazole-3-carboxamide	321.1	> 50	
556	N-(1-(3-aminopropanoyl)piperidin-4-yl)-4H-1,2,4-triazole-3-carboxamide	267.2	> 50	
557	(±)- <i>trans</i> -N-(1-(4-aminocyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)benzamide	344.1	> 10	
558	(±)- <i>cis</i> -N-(1-(4-aminocyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)benzamide	358.1 (+Na)	> 10	
559	N-((1r,4r)-4-aminocyclohexyl)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-c]pyridine-5-carboxamide	275.1	3.49	
560	N-(1-(4-aminobutanoyl)piperidin-4-yl)-4H-1,2,4-triazole-3-carboxamide	281.1	> 10	
561	N-((1r,4r)-4-aminocyclohexyl)-N-methyl-1H-1,2,4-triazole-5-carboxamide	224.1	> 10	
562	N-((1r,4r)-4-aminocyclohexyl)-4-methyl-1H-imidazole-2-carboxamide	223.2	> 10	
563	(±)- <i>trans</i> -N-(1-((3-aminopropyl)sulfonyl)-2-methylpiperidin-4-yl)benzamide	340.05	> 10	
564	(±)- <i>cis</i> -N-(1-((3-aminopropyl)sulfonyl)-2-methylpiperidin-4-yl)benzamide	340.05	> 10	
565	N-((1r,4r)-4-aminocyclohexyl)-6-bromo-2-hydroxyquinoline-3-carboxamide	364	> 10	
566	N-((1r,4r)-4-(3-aminopropanamido)cyclohexyl)-6-bromo-2-hydroxyquinoline-3-carboxamide		> 10	
567	(±)- <i>cis</i> -N-(1-(4-aminocyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)benzamide	366.3 (+Na)	> 10	
568	(±)- <i>cis</i> -N-(1-((3-aminopropyl)sulfonyl)-2-methylpiperidin-4-yl)-[1,1'-biphenyl]-4-carboxamide	438.15 (+Na)	> 10	
569	(±)- <i>cis</i> -N-(1-((3-aminopropyl)sulfonyl)-2-methylpiperidin-4-yl)-3-ethylbenzamide	368.1	8.02	
570	(±)- <i>cis</i> -N-(1-((3-aminopropyl)sulfonyl)-2-methylpiperidin-4-yl)benzamide	340.1	> 10	
571	(±)- <i>trans</i> -N-(1-(4-aminocyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)benzamide	344.1	> 10	
572	2-amino-N-((1r,4r)-4-aminocyclohexyl)-1H-imidazole-4-carboxamide	224.1	> 10	
573	(±)- <i>trans</i> -N-(1-((3-aminopropyl)sulfonyl)-2-methylpiperidin-4-yl)-3-ethylbenzamide	368.2	> 10	
574	N-((1r,4r)-4-aminocyclohexyl)imidazo[1,2-a]pyrimidine-3-carboxamide	260.1	> 10	

* IC₅₀ values are an average of n=1 to n=50

Table 3A

Cpd. No.	Chemical Name	LCMS M+H or (M+Na) or ((M-NH ₂))	SMYD3 Biochem IC ₅₀ (μM)*	SMYD3 cell IC ₅₀ (μM)*
575	N-((1R,3R,5S)-8-(((1r,4R)-4-aminocyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2-oxoindoline-5-carboxamide	447	0.00044	2.17352
576	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-fluoro-2-oxoindoline-5-carboxamide	466	0.00049	0.52547
577	N-((1R,3r,5S)-8-(((1-methylpiperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2-oxoindoline-5-carboxamide	461	0.00067	0.4806
578	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2-oxoindoline-5-carboxamide	448	0.00068	0.85408
579	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-chloro-2-oxoindoline-5-carboxamide	482	0.00081	1.12914
580	N-((2S,4S)-1-((4-aminopiperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-2-oxoindoline-5-carboxamide	436	0.0009	1.63568
581	N-((1R,3r,5S)-8-(((1-(3-hydroxypropyl)piperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2-oxoindoline-5-carboxamide	505	0.00095	1.67455
582	N-((2S,4S)-1-((4-aminopiperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-6-chloro-2-oxoindoline-5-carboxamide	470	0.00098	0.81381
583	N-((1R,3R,5S)-8-(((1r,4R)-4-aminocyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-chloro-2-oxoindoline-5-carboxamide	481	0.0011	1.50735
584	N-((2S)-1-((4-(2-aminopropan-2-yl)phenyl)sulfonyl)-2-methylpiperidin-4-yl)-2-oxoindoline-5-carboxamide	471	0.00147	0.65295

585	6-chloro-N-((1R,3r,5S)-8-(((1-(3-hydroxypropyl)piperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2-oxoindoline-5-carboxamide	539	0.00173	0.76375
586	6-chloro-N-((1R,3r,5S)-8-((4-(methylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2-oxoindoline-5-carboxamide	496	0.00189	0.42454
587	N-((1R,3r,5S)-8-((4-(benzylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2-oxoindoline-5-carboxamide	538	0.00198	0.07099
588	N-((2S,4S)-1-((4-(2-aminopropan-2-yl)phenyl)sulfonyl)-2-methylpiperidin-4-yl)-6-chloro-2-oxoindoline-5-carboxamide	505	0.00198	0.35648
589	N-((1R,3r,5S)-8-((4-(methylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2-oxoindoline-5-carboxamide	462	0.00213	0.98725
590	2-oxo-N-((1R,3r,5S)-8-((piperidin-3-ylmethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)indoline-5-carboxamide	447	0.00214	0.76757
591	N-((1R,3R,5S)-8-(((1s,4S)-4-aminocyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2-oxoindoline-5-carboxamide	447	0.00233	2.31394
592	N-((1R,3r,5S)-8-((4-(benzylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-chloro-2-oxoindoline-5-carboxamide	572	0.00258	0.05357
593	N-((1R,3r,5S)-8-((4-(dimethylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2-oxoindoline-5-carboxamide	476	0.00289	0.50002
594	6-chloro-N-((1R,3r,5S)-8-((4-(dimethylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2-oxoindoline-5-carboxamide	510	0.00346	0.30139

595	6-chloro-2-oxo-N-((1R,3r,5S)-8-(((1-(4,4,4-trifluorobutyl)piperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)indoline-5-carboxamide	591	0.00354	0.03609
596	6-chloro-2-oxo-N-((1R,3r,5S)-8-((piperidin-4-ylmethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)indoline-5-carboxamide	481	0.0036	2.66255
597	2-oxo-N-((1R,3r,5S)-8-((piperidin-4-ylmethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)indoline-5-carboxamide	447	0.00398	3.43731
598	6-chloro-2-oxo-N-((1R,3S,5S)-8-(((S)-piperidin-3-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)indoline-5-carboxamide	481	0.00412	1.26702
599	N-((2S,4S)-2-methyl-1-((piperidin-4-ylmethyl)sulfonyl)piperidin-4-yl)-2-oxoindoline-5-carboxamide	435	0.00442	9.48804
600	6-chloro-2-oxo-N-((1R,3R,5S)-8-(((R)-piperidin-3-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)indoline-5-carboxamide	481	0.00499	0.72841
601	2-oxo-N-((1R,3r,5S)-8-((piperidin-4-ylmethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2,3-dihydrobenzo[d]oxazole-6-carboxamide	449	0.00521	4.54161
602	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-bromo-2-oxoindoline-5-carboxamide	528	0.00712	3.72505
603	N-((3S)-1-((4-aminopiperidin-1-yl)sulfonyl)-3-methylpiperidin-4-yl)-6-chloro-2-oxoindoline-5-carboxamide	470	0.00853	2.67708
604	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-chloro-1-methyl-2-oxoindoline-5-carboxamide	496	0.01347	0.20704
605	N-((2S,4S)-1-((4-aminopiperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-ethylisothiazole-3-carboxamide	416	0.01544	0.20068

606	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-methyl-2-oxoindoline-5-carboxamide	462	0.01561	1.79073
607	N-((2S,4S)-1-((4-aminopiperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropyl-1,3,4-thiadiazole-2-carboxamide	(451)	0.01813	0.20535
608	N-((3R,4R)-1-((4-aminopiperidin-1-yl)sulfonyl)-3-methylpiperidin-4-yl)-6-chloro-2-oxoindoline-5-carboxamide	470	0.02137	6.23686
609	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide	464	0.02365	3.70034
610	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-ethylisothiazole-3-carboxamide	428	0.02378	0.21618
611	1-methyl-2-oxo-N-((1R,3r,5S)-8-((piperidin-4-ylmethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)indoline-5-carboxamide	461	0.02593	3.91552
612	N-((1R,3r,5S)-8-((4-(2-aminopropan-2-yl)phenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2-oxoindoline-5-carboxamide	483	0.03068	2.53133
613	N-((1R,3r,5S)-8-((4-(2-aminopropan-2-yl)phenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-chloro-2-oxoindoline-5-carboxamide	517	0.03712	1.77071
614	6-chloro-2-oxo-N-((1R,3r,5S)-8-((2-(pyrrolidin-1-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)indoline-5-carboxamide	481	0.04599	0.37965
615	2-oxo-N-((1R,3r,5S)-8-((2-(pyrrolidin-1-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)indoline-5-carboxamide	447	0.04974	0.76121
616	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-ethylpyridazine-3-carboxamide	423	0.0499	0.53953

617	6-chloro-1-methyl-2-oxo-N-((1R,3r,5S)-8-((piperidin-4-ylmethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)indoline-5-carboxamide	495	0.05233	2.95866
618	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropyl-1,3,4-thiadiazole-2-carboxamide	441	0.05583	0.3477
619	N-((2S,4S)-1-((4-aminopiperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-ethylpyridazine-3-carboxamide	411	0.05959	0.46793
620	2-oxo-N-(1-((piperidin-4-ylmethyl)sulfonyl)piperidin-4-yl)indoline-5-carboxamide	421	0.06816	10
621	N-(1-((3-aminopropyl)sulfonyl)piperidin-4-yl)-6-chloro-2-oxoindoline-5-carboxamide	415	0.07749	6.83658
622	N-((1R,3r,5S)-8-((4-aminocyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide	472	0.13055	1.07968
623	N-((1R,3R,5S)-8-(((1r,4R)-4-aminocyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide	472	0.1358	0.89555
624	N-(1-((3-aminopropyl)sulfonyl)piperidin-4-yl)-2-oxoindoline-5-carboxamide	381	0.15882	10
625	(R)-2-methyl-3-oxo-N-((1R,3r,5S)-8-((piperidin-4-ylmethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide	477	0.18459	10
626	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide	473	0.22228	2.96871
627	N-((1R,3R,5S)-8-(((1r,4R)-4-(benzylamino)cyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide	562	0.22495	1.54162

628	2,2-difluoro-N-((1R,3r,5S)-8-((piperidin-4-ylmethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)benzo[d][1,3]dioxole-5-carboxamide	472	0.23189	3.62035
629	N-((2S,4R)-1-((4-aminopiperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-ethylisothiazole-3-carboxamide	(438)	0.32589	2.08253
630	2,2-difluoro-N-((1R,3r,5S)-8-(((1-methylpiperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)benzo[d][1,3]dioxole-5-carboxamide	486	0.3614	6.55362
631	N-((2S,4R)-1-((4-aminopiperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropyl-1,3,4-thiadiazole-2-carboxamide	(451)	0.4699	4.89772
632	N-((2S,4S)-1-((4-acetamidophenyl)sulfonyl)-2-methylpiperidin-4-yl)-2-oxoindoline-5-carboxamide	471	0.52572	10
633	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropyl-1H-pyrazole-3-carboxamide	423	0.52917	10
634	N-((3R,4S)-1-((4-aminopiperidin-1-yl)sulfonyl)-3-methylpiperidin-4-yl)-6-chloro-2-oxoindoline-5-carboxamide	470	0.52937	0.97208
635	3-ethyl-N-((1R,3r,5S)-8-((piperidin-4-ylmethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)benzamide	420	0.62038	10
636	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboxamide	464	0.81894	10
637	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-1-cyclopropyl-1H-pyrazole-4-carboxamide	423	0.8386	10
638	N-((1R,3R,5S)-8-((1r,4R)-4-aminocyclohexane-1-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2-oxoindoline-5-carboxamide	411	0.96185	10

639	N-((2S,4S)-1-((4-aminopiperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-1-cyclopropyl-1H-pyrazole-4-carboxamide	411	1.00072	10
640	N-((2S)-1-((1r,4S)-4-aminocyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)-6-chloro-2-oxoindoline-5-carboxamide	((416))	2.04146	10
641	N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)-6-chloro-2-oxoindoline-5-carboxamide	491	5.93159	10
642	N-((2S,4S)-1-((1r,4S)-4-aminocyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)-2-oxoindoline-5-carboxamide	((382))	6.81095	10
643	N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)-2-oxoindoline-5-carboxamide	457	16.85335	10
644	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-cyclopropylisoxazole-5-carboxamide	424.00	0.0185	0.25715

* IC₅₀ values are an average of n=1 to n=50

Table 4A

Cpd. No.	Chemical Name	LCMS M+H	SMYD2 Biochem IC ₅₀ (μM)*
645	5-cyclopropyl-N-[1-(propan-2-yl)azetidin-3-yl]pyridazine-3-carboxamide	261.2	0.74472
646	5-cyclopropyl-N-{1-[(1S)-1-phenylethyl]azetidin-3-yl}pyridazine-3-carboxamide	323.2	0.51586
647	5-cyclopropyl-N-{1-[(1R)-1-phenylethyl]azetidin-3-yl}pyridazine-3-carboxamide	323.2	7.80106
648	N-{1-[(5-chloro-1-methyl-1H-imidazol-4-yl)methyl]azetidin-3-yl}-5-cyclopropylpyridazine-3-carboxamide	347.2	7.32825
649	5-cyclopropyl-N-{1-[1-(2,5-dichlorophenyl)ethyl]azetidin-3-yl}pyridazine-3-carboxamide	391.1	0.14034
650	5-cyclopropyl-N-(1-{1-[3-(2-hydroxyethoxy)-2-methoxyphenyl]ethyl}azetidin-3-yl)pyridazine-3-carboxamide	413.2	0.31235
651	N-(1-benzylazetidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide	309.2	0.54112

652	N-(1-{1-[2-chloro-3-(2-hydroxyethoxy)phenyl]ethyl}azetidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide	417.2	0.04156
657	N-(azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	208.1	10.38816
659	1-cyclopropyl-N-(1-methylazetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	222.1	2.8375
660	1-cyclopropyl-N-(1-propylazetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	250.1	1.16661
661	1-cyclopropyl-N-(1-ethylazetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	236.2	1.57571
662	1-cyclopropyl-N-[1-(propan-2-yl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	250.2	0.84606
663	1-cyclopropyl-N-[1-(propan-2-yl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	250.2	0.58519
664	1-cyclopropyl-N-(1-cyclopropylazetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	248.1	1.48071
665	1-cyclopropyl-N-[1-(cyclopropylmethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	262.2	1.99933
666	1-cyclopropyl-N-[1-(oxetan-3-ylmethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	278.2	6.06091
667	1-cyclopropyl-N-[1-(2-methoxyethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	266.2	2.45794
668	1-cyclopropyl-N-[1-(2-methylpropyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	264.2	2.74698
669	N-[1-(cyclobutylmethyl)azetidin-3-yl]-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	276.2	1.61707
670	1-cyclopropyl-N-[1-(2-hydroxyethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	252.1	4.53271
671	N-(1-benzylazetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	298.1	4.20527
672	N-(1-benzylazetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	298.2	1.55139
673	1-cyclopropyl-N-[1-(2-phenylethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	312.2	1.55399
674	1-cyclopropyl-N-[1-(2-hydroxy-1-phenylethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	328.2	4.27205
675	1-cyclopropyl-N-[1-(1-phenylpropyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	326.2	0.49364
676	N-{1-[1-(4-chlorophenyl)ethyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	346.2	2.18182
677	1-cyclopropyl-N-{1-[1-(2,4-difluorophenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	348.2	2.86259
678	1-cyclopropyl-N-{1-[1-(2-fluorophenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	330.2	0.90683

679	1-cyclopropyl-N-{1-[1-(3-methoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	342.2	1.45146
680	1-cyclopropyl-N-(1-{1-[4-(trifluoromethyl)phenyl]ethyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	380.2	> 50.0
681	N-{1-[1-(4-butoxyphenyl)ethyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	384.2	1.29111
682	1-cyclopropyl-N-{1-[1-(2-methoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	342.3	0.66494
683	1-cyclopropyl-N-{1-[1-(2-methoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	342.3	0.79678
684	1-cyclopropyl-N-(1-{1-[2-(trifluoromethoxy)phenyl]ethyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	396.2	2.13234
685	1-cyclopropyl-N-{1-[1-(pyridin-2-yl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	313.1	3.56033
686	1-cyclopropyl-N-[1-(3-methoxypropyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	280.1	3.76161
687	1-cyclopropyl-N-{1-[1-(3,4-difluorophenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	348.2	2.89677
688	1-cyclopropyl-N-{1-[1-(3,4-dimethoxyphenyl)propan-2-yl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	386.2	5.09675
689	1-cyclopropyl-N-{1-[1-(4-fluoro-2-methoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	360.2	1.88646
690	1-cyclopropyl-N-(1-{1-[2-methoxy-5-(trifluoromethyl)phenyl]ethyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	410.2	7.98548
691	N-{1-[1-(2H-1,3-benzodioxol-5-yl)ethyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	356.2	0.80698
692	N-(1-{1-[4-(benzyloxy)phenyl]ethyl}azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	418.2	0.17228
693	N-(1-{1-[4-(benzyloxy)phenyl]ethyl}azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	418.3	0.17574
694	1-cyclopropyl-N-{1-[1-(4-fluorophenyl)propyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	344.2	0.78735
695	N-{1-[1-(3-chlorophenyl)ethyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	346.1	1.00761
696	1-cyclopropyl-N-{1-[1-(2,5-dichlorophenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	380.1	0.18717

697	1-cyclopropyl-N-{1-[1-(2,5-dichlorophenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	380.1	0.18937
698	1-cyclopropyl-N-{1-[1-(3,4-dimethoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	372.2	3.69446
699	1-cyclopropyl-N-{1-[1-(pyrimidin-5-yl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	314.2	9.54128
700	1-cyclopropyl-N-(1-{1-[4-(trifluoromethyl)phenyl]propyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	394.2	2.66609
701	1-cyclopropyl-N-(1-{[3-(2-methoxyethoxy)phenyl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	372.2	8.02678
702	1-cyclopropyl-N-(1-{1-[3-(2-methoxyethoxy)phenyl]ethyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	386.1	3.57947
703	1-(2-hydroxyethyl)-N-[1-(propan-2-yl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	254.2	> 50.0
704	1-cyclopropyl-N-(1-{1-[3-(2-hydroxyethoxy)phenyl]ethyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	372.2	0.64045
705	1-cyclopropyl-N-[1-(1-{3-[2-(methylamino)ethoxy]phenyl}ethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	385.2	2.04485
706	1-cyclopropyl-N-[1-(1-{3-[2-(dimethylamino)ethoxy]phenyl}ethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	399.2	2.1244
707	1-cyclopropyl-N-[1-(3-hydroxypropyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	266.1	1.91172
708	1-cyclopropyl-N-{1-[3-(dimethylamino)propyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	293.2	> 50.0
709	1-cyclopropyl-N-{1-[(1S)-1-phenylethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	312.2	0.37665
710	N-{1-[1-(2-chloro-4-fluorophenyl)ethyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	364.1	0.34116
711	1-cyclopropyl-N-{1-[1-(3-fluorophenyl)propyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	344.2	1.00729
712	N-(1-{1-[4-chloro-3-(trifluoromethyl)phenyl]ethyl}azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	414.2	7.35557
713	N-[1-(4-chloro-5-methoxy-2,3-dihydro-1H-inden-1-yl)azetidin-3-yl]-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	388.1	12.88746

714	N-{1-[1-(3-chloro-5-fluorophenyl)ethyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	364.1	2.12503
715	1-cyclopropyl-N-{1-[1-(pyrimidin-2-yl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	314.2	1.9389
716	1-cyclopropyl-N-{1-[1-(1,3-thiazol-2-yl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	319.1	30.73955
717	1-cyclopropyl-N-(1-{[1-(2-methoxyethyl)-1H-pyrazol-4-yl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	346.3	3.05744
718	1-cyclopropyl-N-{1-[1-(dimethyl-1,3-thiazol-5-yl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	347.2	2.95156
719	N-[1-(5-chloro-2,3-dihydro-1H-inden-1-yl)azetidin-3-yl]-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	358.2	4.40844
720	1-cyclopropyl-N-{1-[(1R)-1-phenylethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	312.2	23.25339
721	1-cyclopropyl-N-{1-[(1R)-1-phenylpropyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	326.2	4.80835
722	1-cyclopropyl-N-{1-[(1S)-1-phenylpropyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	326.3	0.19827
723	1-(2-aminoethyl)-N-[1-(propan-2-yl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	253.2	> 50.0
724	1-cyclopropyl-N-{1-[1-(4-methoxypyridin-2-yl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	343.2	1.27222
725	1-cyclopropyl-N-{1-[1-(3-methoxypyridin-2-yl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	343.2	1.02479
726	1-cyclopropyl-N-(1-{[3-(methylcarbamoyl)phenyl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	355.2	10.70724
727	N-{1-[(3-carbamoylphenyl)methyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	341.1	7.29596
728	1-cyclopropyl-N-(1-{1-[4-(morpholin-4-yl)phenyl]ethyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	397.2	0.75494
729	1-cyclopropyl-N-{1-[2,2,2-trifluoro-1-(3-methoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	396.2	> 50.0
730	1-cyclopropyl-N-{1-[1-(3-phenoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	404.2	3.04417
731	N-{1-[cyclobutyl(phenyl)methyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	352.2	1.51599

732	1-cyclopropyl-N-{1-[1-(4-fluoro-3-methoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	360.2	2.58965
733	1-cyclopropyl-N-{1-[(1-methyl-1H-imidazol-4-yl)methyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	302.2	6.80081
734	1-cyclopropyl-N-(1-{[3-(2-hydroxyethoxy)phenyl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	358.2	2.30886
735	1-cyclopropyl-N-[1-({3-[2-(methylamino)ethoxy]phenyl}methyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	371.2	2.33404
736	1-cyclopropyl-N-[1-({3-[2-(dimethylamino)ethoxy]phenyl}methyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	385.2	2.80792
737	N-(1-{1-[3-(benzyloxy)phenyl]ethyl}azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	418.3	0.71843
738	1-cyclopropyl-N-[1-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	368.3	5.82879
739	1-cyclopropyl-N-{1-[1-(4-phenoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	404.2	1.07309
740	1-cyclopropyl-N-[1-(5-fluoro-2,3-dihydro-1H-inden-1-yl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	342.2	6.96336
741	1-cyclopropyl-N-(1-{1-[2-(trifluoromethyl)phenyl]ethyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	380.2	1.00727
742	1-cyclopropyl-N-{1-[1-(2,6-difluorophenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	348.2	2.84963
743	1-cyclopropyl-N-{1-[1-(2,3-dichlorophenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	380.2	0.48846
744	1-cyclopropyl-N-[1-(4,5-dimethoxy-2,3-dihydro-1H-inden-1-yl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	384.2	23.71632
745	1-cyclopropyl-N-{1-[1-(pyrazin-2-yl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	314.1	7.44095
746	1-cyclopropyl-N-{1-[1-(2,5-difluorophenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	348.2	7.77636
747	1-cyclopropyl-N-{1-[1-(4-fluorophenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	330.2	1.92161
748	1-cyclopropyl-N-(1-{1-[3-(trifluoromethyl)phenyl]ethyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	380.2	2.80977

749	1-cyclopropyl-N-{1-[2,2,2-trifluoro-1-(4-methoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	396.1	0.56478
750	1-cyclopropyl-N-{1-[1-(2-hydroxy-6-methoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	358.2	1.27817
751	1-cyclopropyl-N-{1-[1-(1,3-thiazol-2-yl)propyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	333.2	20.98439
752	1-cyclopropyl-N-[1-(2-methoxy-1-phenylethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	342.2	6.09419
753	1-cyclopropyl-N-[1-({3-[(methylamino)methyl]phenyl}methyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	341.3	15.98565
754	N-(1-{[3-(aminomethyl)phenyl]methyl}azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	327.2	7.33653
755	1-cyclopropyl-N-[1-(1-phenylcyclopropyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	324.2	30.45617
756	1-cyclopropyl-N-[1-({1-[2-(methylamino)ethyl]-2-oxopyrrolidin-3-yl}methyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	362.3	17.04064
757	1-cyclopropyl-N-[1-(2-phenylpropan-2-yl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	326.2	3.8847
758	1-cyclopropyl-N-(1-{[4-(methylamino)oxan-2-yl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	335.3	> 50.0
759	1-cyclopropyl-N-[1-(1-phenylpropan-2-yl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	326.2	1.39034
760	1-cyclopropyl-N-{1-[1-(4-fluorophenyl)-2-methylpropyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	358.2	3.27451
761	1-cyclopropyl-N-{1-[1-(1H-indazol-3-yl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	352.2	3.21089
762	1-cyclopropyl-N-[1-(7-methoxy-2,3-dihydro-1H-inden-1-yl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	354.3	7.97221
763	1-cyclopropyl-N-{1-[1-(2,3-dimethoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	372.2	0.08855
764	1-cyclopropyl-N-{1-[1-(2,3-dimethoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	372.2	0.09346
765	1-cyclopropyl-N-{1-[(3-oxo-2,3-dihydro-1H-isoindol-5-yl)methyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	353.1	10.21303

766	1-cyclopropyl-N-[1-(2,2,2-trifluoro-1-phenylethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	366.2	> 50.0
767	1-cyclopropyl-N-{1-[1-(2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	370.1	0.57587
768	1-cyclopropyl-N-{1-[1-(2,6-dimethoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	372.3	1.68248
769	1-cyclopropyl-N-{1-[1-(2,6-dichlorophenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	380.1	1.19872
770	1-(2,2-difluorocyclopropyl)-N-[1-(propan-2-yl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	286.2	4.19117
771	1-cyclopropyl-N-[1-(1-{3-[(methylamino)methyl]phenyl}ethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	355.2	4.98252
772	1-cyclopropyl-N-(1-{[3-(hydroxymethyl)-2-methoxyphenyl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	358.2	10.81324
773	1-cyclopropyl-N-[1-(2-methanesulfonyl-1-phenylethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	390.1	> 50.0
774	1-cyclopropyl-N-{1-[1-(3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	383.2	1.61549
775	N-(1-{1-[2-chloro-3-(2-hydroxyethoxy)phenyl]ethyl}azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	406.2	0.04944
776	1-cyclopropyl-N-(1-{1-[3-(2-hydroxyethoxy)-2-methoxyphenyl]ethyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	402.2	0.34533
777	1-cyclopropyl-N-{1-[(3-methoxy-1-methyl-1H-pyrazol-4-yl)methyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	332.2	5.61969
778	rel-N-{1-[(1R)-1-[4-(benzyloxy)phenyl]ethyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	418.2	0.08453
779	rel-1-cyclopropyl-N-{1-[(1R)-1-(2,5-dichlorophenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	380.1	0.10953
780	rel-1-cyclopropyl-N-{1-[(1R)-1-(2-methoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	342.3	0.3468
781	1-cyclopropyl-N-[1-(3-phenyloxetan-3-yl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	340.2	> 50.0

782	1-cyclopropyl-N-(1-{[1-(2-phenylethyl)-1H-imidazol-4-yl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	392.4	2.61584
783	1-cyclopropyl-N-{1-[1-(3-acetamidophenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	369.1	3.13518
784	N-{1-[(5-chloro-1-methyl-1H-imidazol-4-yl)methyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	336.2	21.02524
785	1-cyclopropyl-N-{1-[1-(1H-imidazol-4-yl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	302.2	2.594
786	1-cyclopropyl-N-{1-[cyclopropyl(4-fluorophenyl)methyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	356.1	1.70115
787	1-cyclopropyl-N-[1-(2-methyl-1-phenylpropyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	340.3	1.42952
788	rel-N-{1-[(1R)-1-[4-(benzyloxy)phenyl]ethyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide		0.4137
789	rel-1-cyclopropyl-N-{1-[(1R)-1-(2,5-dichlorophenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide		31.57011
790	rel-1-cyclopropyl-N-{1-[(1R)-1-(2-methoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide		28.78884
791	1-cyclopropyl-N-{1-[1-(pyridin-2-yl)propyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	327.1	2.47462
792	N-{1-[(1-benzyl-1H-pyrazol-4-yl)methyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	378.2	0.01635
793	1-cyclopropyl-N-[1-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	368.2	9.91987
794	N-(1-{[3-(aminomethyl)-2-methoxyphenyl]methyl}azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	357.3	32.30456
795	N-{1-[(1-benzyl-1H-imidazol-4-yl)methyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	378.3	7.14819
796	N-(1-{1-[2-(benzyloxy)phenyl]ethyl}azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	418.2	0.4215
797	1-cyclopropyl-N-(1-{1-[4-(1H-imidazol-1-yl)phenyl]ethyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	378.1	1.56764

798	1-cyclopropyl-N-{1-[1-(2-fluorophenyl)propyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	344.2	0.42506
799	1-cyclopropyl-N-[2,2-dimethyl-1-(propan-2-yl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	278.2	9.59545
800	N-(1-{1-[4-(benzyloxy)-2-methoxyphenyl]ethyl}azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	448.3	0.96532
801	1-cyclopropyl-N-{1-[1-(2,4-dimethoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	372.3	1.05608
802	N-(1-{[4-(benzyloxy)phenyl]methyl}azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	404.2	0.08341
803	N-{1-[1-(2-chloro-3-methoxyphenyl)ethyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	376.2	0.06945
804	rel-1-cyclopropyl-N-{1-[(1R)-1-(2,3-dimethoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	372.2	0.04426
805	rel-1-cyclopropyl-N-{1-[(1S)-1-(2,3-dimethoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide		42.35178
806	1-cyclopropyl-N-(1-{[1-(2-phenylethyl)-1H-pyrazol-4-yl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	392.2	0.97043
807	5-cyclopropyl-N-(1-{[1-(2-phenylethyl)-1H-pyrazol-4-yl]methyl}azetidin-3-yl)pyridazine-3-carboxamide	403.2	0.52752
808	1-cyclopropyl-N-[1-(propan-2-yl)piperidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	278.2	19.78446
809	N-{1-[(1-benzyl-1H-imidazol-5-yl)methyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	378.3	> 50.0
810	1-cyclopropyl-N-(1-{[1-(2-phenylethyl)-1H-imidazol-5-yl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	392.3	9.28801
811	N-{1-[(3-chloro-1-methyl-1H-pyrazol-4-yl)methyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	336.1	1.2247
812	1-cyclopropyl-N-[1-({2-methoxy-3-[(methylamino)methyl]phenyl}methyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	371.2	41.20464
813	1-cyclopropyl-N-{1-[1-(4-fluorophenyl)-2-hydroxyethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	346.2	15.19205
814	5-cyclopropyl-N-(1-ethylazetidin-3-yl)pyridazine-3-carboxamide	247.2	0.59765
815	5-cyclopropyl-N-[1-(propan-2-yl)piperidin-3-yl]pyridazine-3-carboxamide	289.2	18.67277

816	N-(1-{1-[4-(benzyloxy)phenyl]-2,2,2-trifluoroethyl}azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	472.3	> 50.0
817	N-(1-{1-[4-(benzyloxy)-2-chlorophenyl]ethyl}azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	452.2	0.10155
818	1-cyclopropyl-N-(1-{[4-(3-methoxypropoxy)phenyl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	386.3	3.00034
819	1-cyclopropyl-N-(1-{[4-(2,3-dihydroxypropoxy)phenyl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	388.2	1.99348
820	N-(5-hydroxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-7-yl)-3-(methylamino)cyclohexane-1-carboxamide	320	> 50.0
821	1-cyclopropyl-N-{1-[1-(4-methoxyphenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	342.3	0.78452
822	1-cyclopropyl-N-(1-{[4-(2-hydroxypropoxy)phenyl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	372.3	1.96551
823	1-cyclopropyl-N-(1-{[4-(3-hydroxypropoxy)phenyl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	372.2	3.21621
824	1-cyclopropyl-N-{1-[1-(4-hydroxyphenyl)methyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	314.1	0.88212
825	5-cyclopropyl-N-(1-methylazetidin-3-yl)pyridazine-3-carboxamide	233.2	0.39067
826	1-cyclopropyl-N-{1-[1-(4-methoxyphenyl)methyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	328.2	1.83875
827	1-cyclopropyl-N-(1-{[4-(2-hydroxyethoxy)phenyl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	358.3	1.37605
828	1-cyclopropyl-N-(1-{[4-(pyridin-4-ylmethoxy)phenyl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	405.2	1.03298
829	1-cyclopropyl-N-[1-(1-{4-[2-(morpholin-4-yl)-2-oxoethoxy]phenyl}ethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	455.3	0.71252
830	1-cyclopropyl-N-(1-{[4-(2-methoxyethoxy)phenyl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	372.3	2.06713
831	rel-N-{1-[(1S)-1-[2-chloro-3-(2-hydroxyethoxy)phenyl]ethyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	406.2	0.05775

832	rel-N-{1-[(1R)-1-[2-chloro-3-(2-hydroxyethoxy)phenyl]ethyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	406.2	14.28102
833	N-{1-[(3-chloro-1-methyl-1H-pyrazol-4-yl)methyl]azetidin-3-yl}-5-cyclopropylpyridazine-3-carboxamide	347.1	0.94017
834	1-cyclopropyl-N-[2-(dimethylamino)ethyl]-1H-1,2,3-triazole-4-carboxamide	224.3	> 50.0
835	1-cyclopropyl-N-[1-(1-{2-methoxy-3-[(methylamino)methyl]phenyl}ethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	385.3	0.77956
836	N-(1-{1-[4-(benzyloxy)phenyl]ethyl}azetidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide	429.3	0.02651
837	N-{1-[(1S)-1-(3-chlorophenyl)propyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	360.3	0.33977
838	5-cyclopropyl-N-(1-{[1-(2-phenylethyl)-1H-imidazol-4-yl]methyl}azetidin-3-yl)pyridazine-3-carboxamide	403.3	0.49607
839	N-[1-(azetidin-3-yl)ethyl]-5-cyclopropylpyridazine-3-carboxamide	247.2	18.24266
840	5-cyclopropyl-N-{1-[1-(propan-2-yl)azetidin-3-yl]ethyl}pyridazine-3-carboxamide	289.2	36.83929
841	5-cyclopropyl-N-{1-[(1S)-1-(2-methoxyphenyl)ethyl]azetidin-3-yl}pyridazine-3-carboxamide	353.3	5.00737
842	5-cyclopropyl-N-{1-[(1R)-1-(2-methoxyphenyl)ethyl]azetidin-3-yl}pyridazine-3-carboxamide	353.3	0.18913
843	(±)- <i>cis</i> -N-(1-{[3-(benzyloxy)cyclobutyl]methyl}azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	382.2	1.15555
844	1-cyclopropyl-N-[1-(1-{4-[2-oxo-2-(piperidin-1-yl)ethoxy]phenyl}ethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	453.3	1.54771
845	N-{1-[1-(2-chloro-4-methoxyphenyl)ethyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	376.2	0.08798
846	1-cyclopropyl-N-(1-{[4-(1,3-thiazol-4-ylmethoxy)phenyl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	411.2	1.08508
847	N-[1-(1-{4-[(3-chlorophenyl)methoxy]phenyl}ethyl)azetidin-3-yl]-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	452.2	0.27389
848	N-[1-(1-{4-[(4-chlorophenyl)methoxy]phenyl}ethyl)azetidin-3-yl]-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	452.2	0.06933

849	1-cyclopropyl-N-(1-{[4-(pyridin-2-ylmethoxy)phenyl]methyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	405.1	2.66119
850	1-cyclopropyl-N-(1-{1-[4-(piperidin-3-ylmethoxy)phenyl]ethyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	425.2	3.32842
851	N-{1-[1-(2-chloro-3-methoxyphenyl)ethyl]azetidin-3-yl}-5-cyclopropylpyridazine-3-carboxamide	387.2	0.07206
852	(±)- <i>trans</i> - N-(1-{[3-(benzyloxy)cyclobutyl]methyl}azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	382.3	0.98162
853	1-cyclopropyl-N-(1-{1-[4-(2-phenylethoxy)phenyl]ethyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	432.3	0.77613
854	1-cyclopropyl-N-{1-[1-(4-{[4-(methylcarbamoyl)phenyl]methoxy}phenyl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	475.3	0.96536
855	1-cyclopropyl-N-[1-(1-{4-[(4-methoxyphenyl)methoxy]phenyl}ethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	448.3	0.15904
856	5-cyclopropyl-N-{1-[1-(4-methoxyphenyl)ethyl]azetidin-3-yl}pyridazine-3-carboxamide	353.2	0.60267
857	1-cyclopropyl-N-[1-(1-{4-[2-(dimethylamino)ethoxy]phenyl}ethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	399.2	1.97865
858	1-cyclopropyl-N-[1-(1-{4-[3-(dimethylamino)propoxy]phenyl}ethyl)azetidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	413.2	4.79409
859	N-{1-[1-(2-chlorophenyl)ethyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	346.2	0.16007
860	N-{1-[1-(5-chloro-2-methoxyphenyl)ethyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	376.2	2.79163
861	5-cyclopropyl-N-{1-[1-(2,3-dimethoxyphenyl)ethyl]azetidin-3-yl}pyridazine-3-carboxamide	383.2	0.12148
862	N-(1-{1-[4-(benzylamino)phenyl]ethyl}azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	417.3	0.334
863	N-{1-[1-(4-benzamidophenyl)ethyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	431.3	1.73815
864	1-cyclopropyl-N-(1-{1-[4-(2,2-dimethylpropoxy)phenyl]ethyl}azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	398.3	3.14078
865	1-cyclopropyl-N-{1-[1-(5-methoxypyrimidin-2-yl)ethyl]azetidin-3-yl}-1H-1,2,3-triazole-4-carboxamide	344.2	1.6379

866	N-{1-[(1S)-1-(3-chlorophenyl)propyl]azetidin-3-yl}-5-cyclopropylpyridazine-3-carboxamide	371.2	0.35518
867	5-cyclopropyl-N-[3-(dimethylamino)propyl]pyridazine-3-carboxamide	249.2	> 50.0
868	N-(1-{1-[4-(benzyloxy)-3-chlorophenyl]ethyl}azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	452.2	0.92507
869	5-cyclopropyl-N-[2-(dimethylamino)ethyl]pyridazine-3-carboxamide	235.2	21.10972
913	5-cyclopropyl-N-[1-(propan-2-yl)azetidin-3-yl]-1H-imidazole-2-carboxamide	249.2	1.69797
914	5-cyclopropyl-N-{1-[(1S)-1-phenylethyl]azetidin-3-yl}-1H-imidazole-2-carboxamide	311.2	0.72872
915	5-cyclopropyl-N-{1-[(1R)-1-phenylethyl]azetidin-3-yl}-1H-imidazole-2-carboxamide	311.2	> 50.0
916	5-cyclopropyl-N-[1-(propan-2-yl)piperidin-4-yl]pyridazine-3-carboxamide	289.3	29.10492
917	5-cyclopropyl-N-(1-methylpiperidin-4-yl)pyridazine-3-carboxamide	261.2	> 50.0
918	5-cyclopropyl-N-(1-methylpiperidin-3-yl)pyridazine-3-carboxamide	261.3	> 50.0

* IC₅₀ values are an average of n=1 to n=50

Table 6A

Cpd. No.	Chemical Name	LCMS M+H	SMYD2 Biochem IC ₅₀ (μM)*
919	1-cyclopropyl-N-(1-isopropylazetidin-3-yl)-1H-imidazole-4-carboxamide	249.2	4.6
920	N-(1-(1-(3-(2-chlorophenyl)-1H-indazol-5-yl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	462.2	> 50
921	1-cyclopropyl-N-(3-(dimethylamino)propyl)-1H-1,2,3-triazole-4-carboxamide	238.3	5.4
922	1-cyclopropyl-N-(1-(1-(4-((phenylamino)methyl)phenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	417.2	0.65
923	1-cyclopropyl-N-(1-(1-(5-methoxypyridin-2-yl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	343.3	2.7
924	1-cyclopropyl-N-(1-((6-(phenylamino)pyridin-3-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	390.2	
925	1-cyclopropyl-N-(1-(1-(4-(piperidin-4-ylmethoxy)phenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	425.3	4.3

926	N-(1-((6-(benzylamino)pyridin-3-yl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	404.2	
927	N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-4-cyclopropyl-1H-imidazole-2-carboxamide	411.2	0.011
928	5-cyclopropyl-N-(1-(4-((1-methyl-1H-pyrazol-4-yl)methoxy)benzyl)azetidin-3-yl)pyridazine-3-carboxamide	419.3	0.61
929	N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide	423.2	0.0012
930	N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-4-cyclopropylpicolinamide	422.7	0.0033
931	N-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	379.3	11.1
932	1-cyclopropyl-N-(1-((1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	408.2	0.028
933	N-(1-((1-benzyl-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide	389.2	0.0078
934	5-cyclopropyl-N-(1-(1-(3-methoxyphenyl)ethyl)azetidin-3-yl)pyridazine-3-carboxamide	353.2	0.69
935	1-cyclopropyl-N-(1-(1-(2-methyl-2H-indazol-5-yl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	366.2	1.6
936	N-(1-((1-(benzo[d]thiazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	435.2	0.080
937	1-cyclopropyl-N-(1-((1-((4-methyloxazol-2-yl)methyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	383.2	0.12
938	N-(1-(1-(2-chloro-5-methoxyphenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	376.2	0.13
939	N-(1-(1-(4-(benzyloxy)-3-methoxyphenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	448.3	3.6
940	N-(1-((1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	288.2	7.7
941	1-cyclopropyl-N-(1-((1-(4-(methylthio)benzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	424.2	0.028
942	N-(1-((1-(2-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	412.1	0.11
943	1-cyclopropyl-N-(1-((1-(4-(trifluoromethyl)benzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-	446.2	0.014

	triazole-4-carboxamide		
944	1-cyclopropyl-N-(1-((1-(oxazol-2-ylmethyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	369.2	0.92
945	1-cyclopropyl-N-(1-((1-(thiazol-4-ylmethyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	385.2	1.2
946	1-cyclopropyl-N-(1-((1-ethyl-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	316.2	2.0
947	N-(1-((1-(4-(tert-butyl)benzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	434.3	0.056
948	N-(1-((1-(cyclohexylmethyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	384.3	0.36
949	1-cyclopropyl-N-(1-((1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	386.2	2.4
950	1-cyclopropyl-N-(1-((1-((tetrahydrofuran-3-yl)methyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	372.3	2.0
951	1-cyclopropyl-N-(1-((1-(4-fluorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	396.2	0.022
952	1-cyclopropyl-N-(1-(1-(1-methyl-1H-indazol-5-yl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	366.2	1.63
953	N-(1-(4-((1H-pyrazol-1-yl)methyl)benzyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	378.3	5.6
954	N-(1-(4-((1H-pyrazol-1-yl)methyl)benzyl)azetidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide	389.3	2.4
955	N-(1-((1-benzyl-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-5-cyclopropylisoxazole-3-carboxamide	378.2	0.073
956	N-(1-(1-(2-chloro-3-(2-hydroxy-2-methylpropoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	434.2	2.6
957	1-cyclopropyl-N-(1-(1-(4-((4-methoxybenzyl)oxy)phenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	448.3	0.16
958	5-cyclopropyl-N-(1-(1-(4-methoxyphenyl)ethyl)azetidin-3-yl)pyridazine-3-carboxamide	353.2	0.60
959	1-cyclopropyl-N-(1-(1-(4-(2-(dimethylamino)ethoxy)phenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	399.2	2.0
960	1-cyclopropyl-N-(1-(1-(4-phenethoxyphenyl)ethyl)azetidin-3-yl)-1H-1,2,3-	432.3	0.78

	triazole-4-carboxamide		
961	4-cyclopropyl-N-(1-isopropylazetidin-3-yl)picolinamide	260.2	1.3
962	4-cyclopropyl-N-(1-(1-(2,5-dichlorophenyl)ethyl)azetidin-3-yl)picolinamide	390.1	0.48
963	1-cyclopropyl-N-(1-(1-(4-((4-(methylcarbamoyl)benzyl)oxy)phenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	475.3	0.97
964	N-(1-(1-(2-chloro-3-(2-hydroxyethoxy)phenyl)ethyl)azetidin-3-yl)-4-cyclopropylpicolinamide	416.2	10.5
965	N-(1-(1-(2-chloro-3-methoxyphenyl)ethyl)azetidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide	387.2	0.072\
966	N-(1-((1-benzyl-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-4-cyclopropylpicolinamide	388.3	0.013
967	N-(1-(4-(benzyloxy)benzyl)azetidin-3-yl)-4-cyclopropylpicolinamide	414.2	0.15
968	1-cyclopropyl-N-(1-(1-(4-(2,2,2-trifluoroethoxy)phenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	410.2	1.7
969	rac-N-(1-(((1r,3r)-3-(benzyloxy)cyclobutyl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	382.3	0.98
970	N-(1-(1-(5-chloro-2-(difluoromethoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	412.2	5.1
971	1-cyclopropyl-N-(1-(1-(4-((4-methylbenzyl)oxy)phenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	432.3	0.088
972	1-cyclopropyl-N-(1-(4-(pyridin-3-ylmethoxy)benzyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	405.3	1.3
973	N-(1-(1-(2-chloro-3-(2,3-dihydroxypropoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	436.2	> 50
974	1-cyclopropyl-N-(1-(1-(4-(phenoxymethyl)phenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	418.3	0.87
975	N-(1-(1-(2-chloro-3-(2-(methylamino)ethoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	419.3	5.4
976	N-(1-(1-(5-chloro-2-(trifluoromethyl)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	414.2	1.8
977	N-(1-(1-(2-chloro-3-(2-(dimethylamino)ethoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	433.2	7.5
978	N-(1-(1-(2-chloro-3-(2-	420.2	1.1

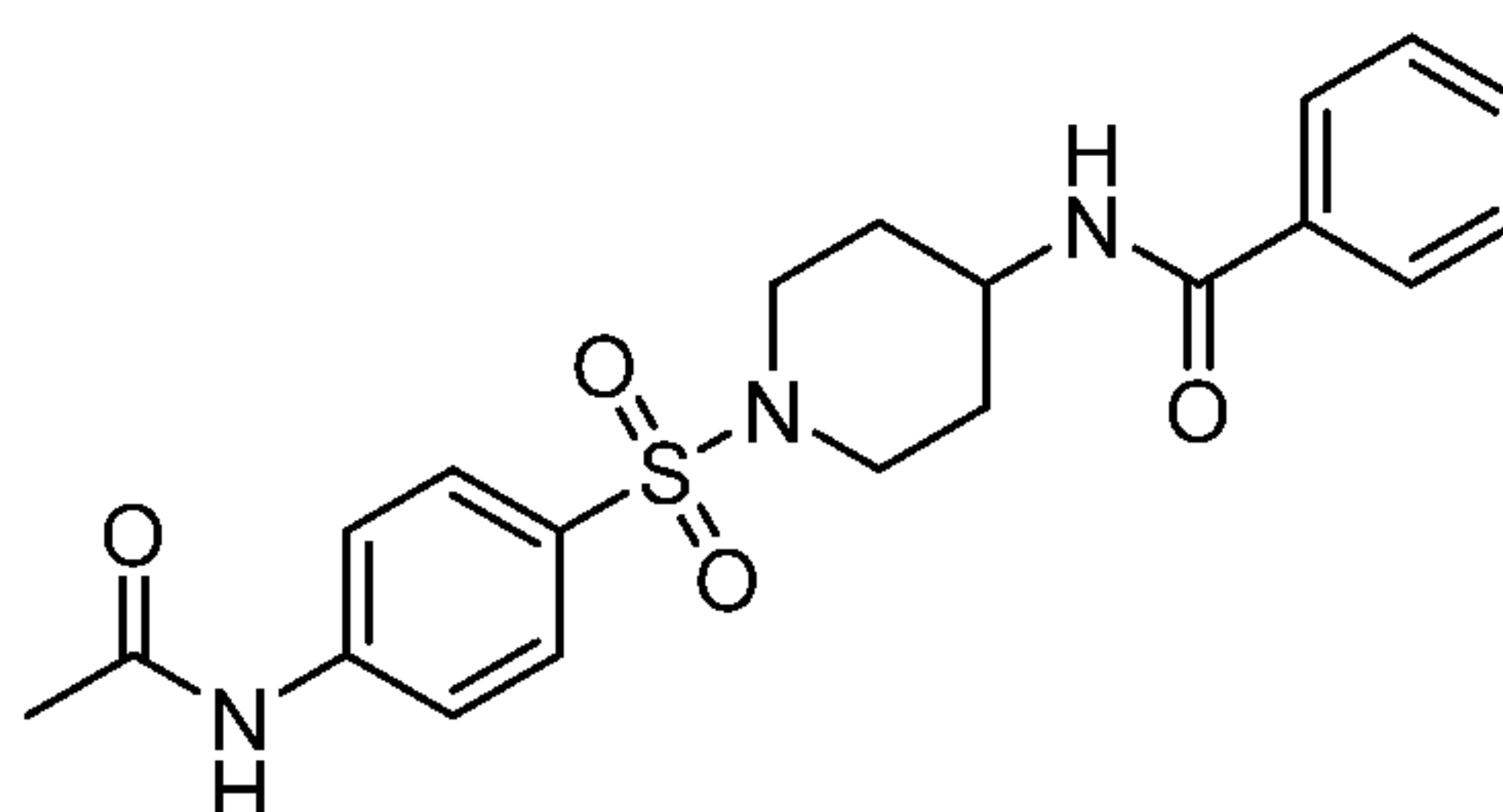
	hydroxypropoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide		
979	1-cyclopropyl-N-(1-(1-methylpiperidin-2-yl)ethyl)-1H-1,2,3-triazole-4-carboxamide	278.2	> 50
980	N-(1-(2-(4-(benzyloxy)phenyl)propan-2-yl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	432.3	0.99
981	5-cyclopropyl-N-(1-(1-methylpiperidin-2-yl)ethyl)pyridazine-3-carboxamide	289.2	> 50
982	1-cyclopropyl-N-(1-((1-(3-methoxybenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	408.3	0.169
983	1-cyclopropyl-N-(1-(4-(1-hydroxy-2-phenylethyl)benzyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	418.2	1.39
984	rac-1-cyclopropyl-N-((R)-2,2-dimethyl-1-((R)-1-phenylethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	340.2	18.9
985	N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	412.2	0.0039
986	N-(1-((1-benzyl-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-5-cyclopropyl-1H-imidazole-2-carboxamide	377.3	> 50
987	N-(1-((1-(3-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	412.2	0.024
988	N-(1-(4-((1,3,4-thiadiazol-2-yl)methoxy)benzyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	412.2	1.9
989	N-(1-(1-(5-chloro-2-(4-fluorophenoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	456.2	> 50.0
990	1-cyclopropyl-N-(1-(1-(4-(piperidin-3-ylmethoxy)phenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	425.2	3.3
991	1-cyclopropyl-N-(1-((1-(thiazol-2-ylmethyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	385.2	0.76
992	1-cyclopropyl-N-(1-(4-(pyridin-2-ylmethoxy)benzyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	405.1	2.7
993	1-cyclopropyl-N-(1-((1-(4-methylbenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	392.3	0.016
994	1-cyclopropyl-N-(1-(1-(6-oxo-1,6-dihydropyridin-3-yl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	329.2	5.4
995	1-cyclopropyl-N-(1-((1-(2-methoxybenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-	408.2	1.3

	4-carboxamide		
996	N-(1-(1-(4-((4-chlorobenzyl)oxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	452.2	0.069
997	N-(1-(1-(4-((3-chlorobenzyl)oxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	452.2	0.27
998	1-cyclopropyl-N-(1-((1-isobutyl-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	343.4	2.4
999	1-cyclopropyl-N-(1-(4-(thiazol-4-ylmethoxy)benzyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	411.2	1.1
1000	1-cyclopropyl-N-(1-(piperidin-2-yl)ethyl)-1H-1,2,3-triazole-4-carboxamide	264.1	> 50
1001	N-(1-((1-(cyclobutylmethyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	356.2	1.4
1002	N-(1-(1-(2-chloro-4-methoxyphenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	376.2	0.088
1003	5-cyclopropyl-N-(1-(piperidin-2-yl)ethyl)pyridazine-3-carboxamide	275.2	19.0
1004	1-cyclopropyl-N-(1-(1-(4-(2-oxo-2-(piperidin-1-yl)ethoxy)phenyl)ethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	453.3	1.5
1005	4-cyclopropyl-N-(1-(1-(2,3-dimethoxyphenyl)ethyl)azetidin-3-yl)picolinamide	381.9	0.13
1006	1-cyclopropyl-N-(1-((1-(cyclopropylmethyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	342.2	1.7
1007	N-(1-((1-benzyl-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-5-cyclopropyl-1,3,4-thiadiazole-2-carboxamide	395.1	0.072
1008	rac-N-(1-(((1s,3s)-3-(benzyloxy)cyclobutyl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	382.2	1.2
1009	N-(1-(1-(3-(2-aminoethoxy)-2-chlorophenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	405.3	5.7
1012	N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-imidazole-4-carboxamide	411.1	
1017	1-cyclopropyl-N-(1-((1-((1-methyl-1H-pyrazol-4-yl)methyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	382.2	
1020	N-(1-(1-(4-((4-acetamidobenzyl)oxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	475.3	0.95
1021	N-(1-((1-benzyl-1H-pyrazol-4-yl)methyl)azetidin-3-	379.2	0.065

	yl)-5-cyclopropyl-1,3,4-oxadiazole-2-carboxamide		
1022	N-(1-((1-benzyl-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-imidazole-4-carboxamide	377.2	0.073
1023	5-cyclopropyl-N-((1R,3s,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)pyridazine-3-carboxamide	287.2	6.3
1024	5-cyclopropyl-N-((1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)pyridazine-3-carboxamide	287.2	> 50
1025	1-cyclopropyl-N-(1-(4-((1-methyl-1H-pyrazol-4-yl)methoxy)benzyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	408.3	1.2
1026	rac-1-cyclopropyl-N-((R)-2,2-dimethyl-1-((S)-1-phenylethyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	340.3	0.91
1028	N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-5-cyclopropyl-1,3,4-oxadiazole-2-carboxamide	413.2	

* IC₅₀ values are an average of n=1 to n=50

[0104] In another embodiment, a Compound of the Disclosure is a compound having Formulae **I-XVIII**, provided that the compound is not N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)benzamide:



[0105] In some embodiments, the disclosure relates to pharmaceutical compositions comprising N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)benzamide and a pharmaceutically acceptable carrier.

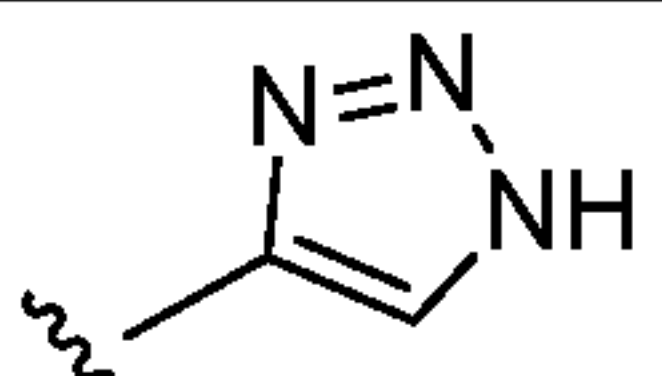
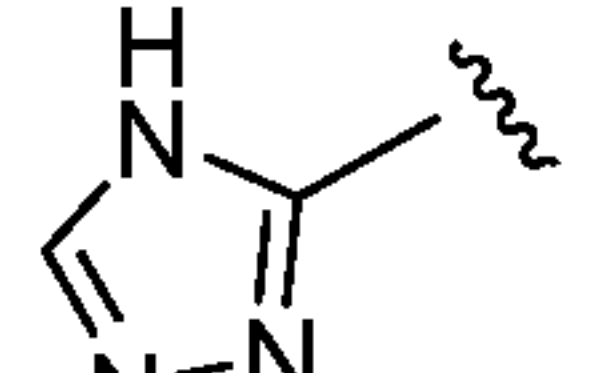
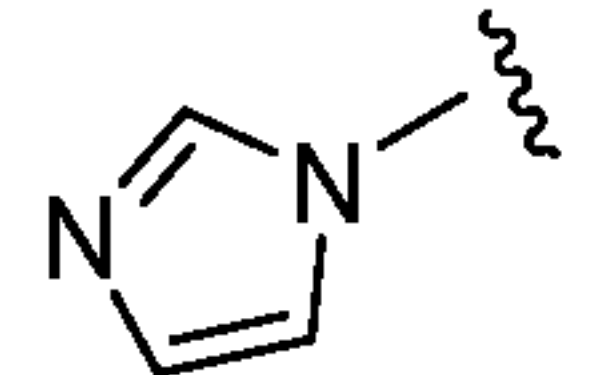
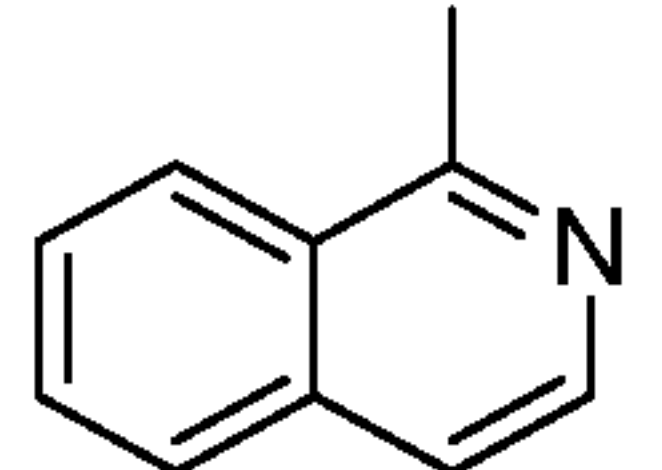
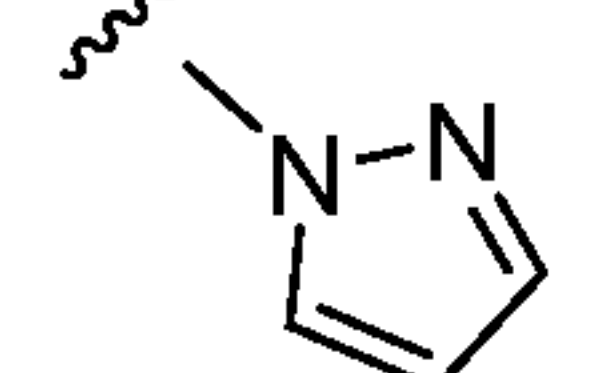
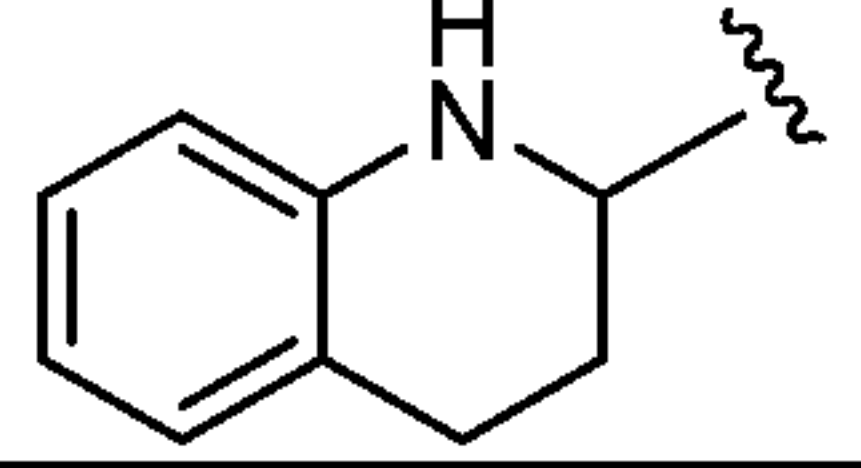
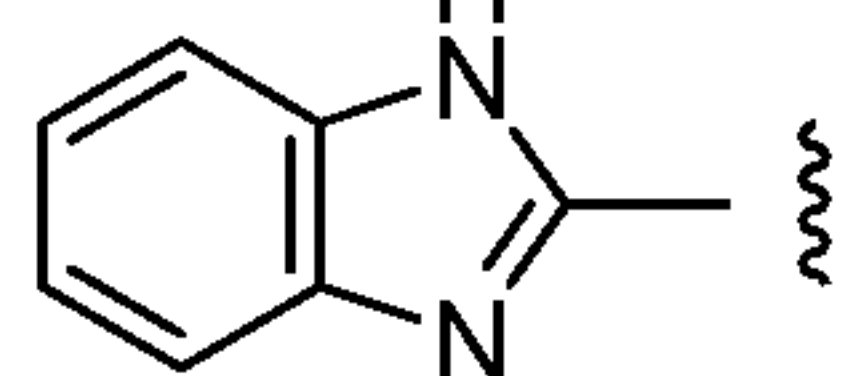
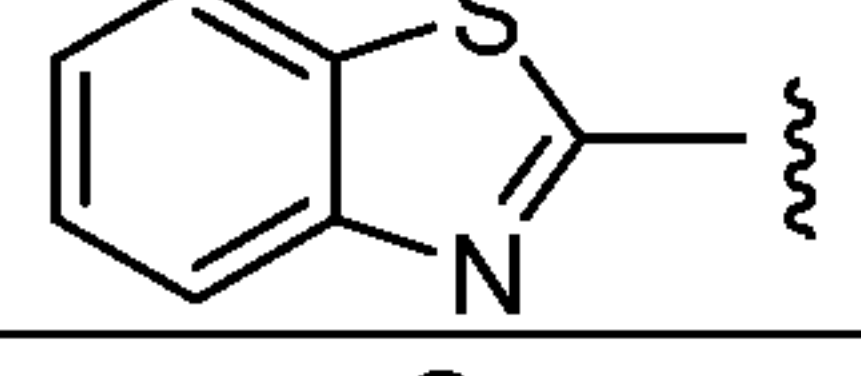
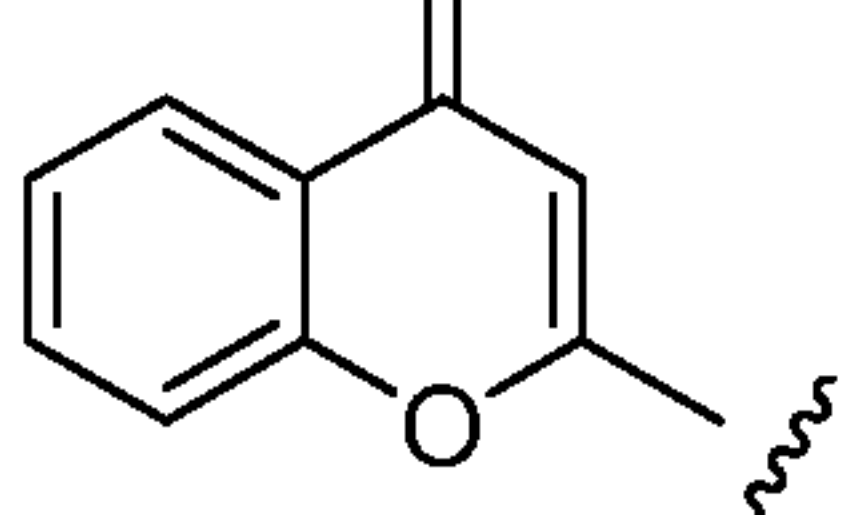
[0106] In some embodiments, the disclosure relates to a method of inhibiting SMYD proteins, such as SMYD3 or SMYD2, or both, in a subject, comprising administering to a subject in need thereof an effective amount of N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)benzamide.

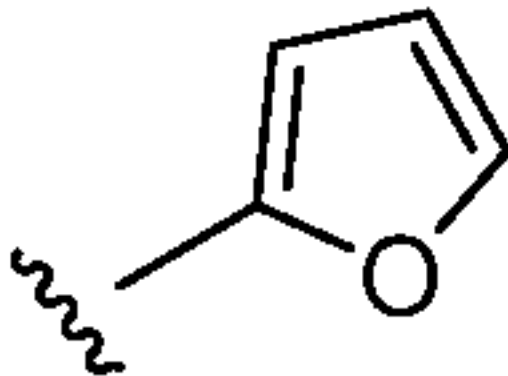
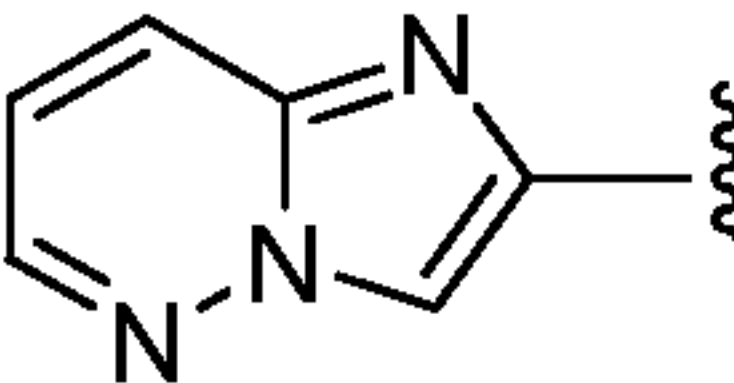
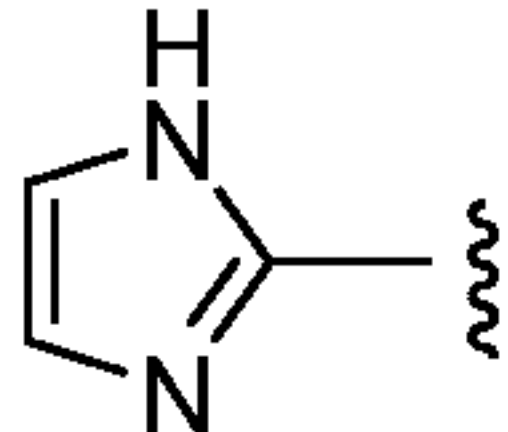
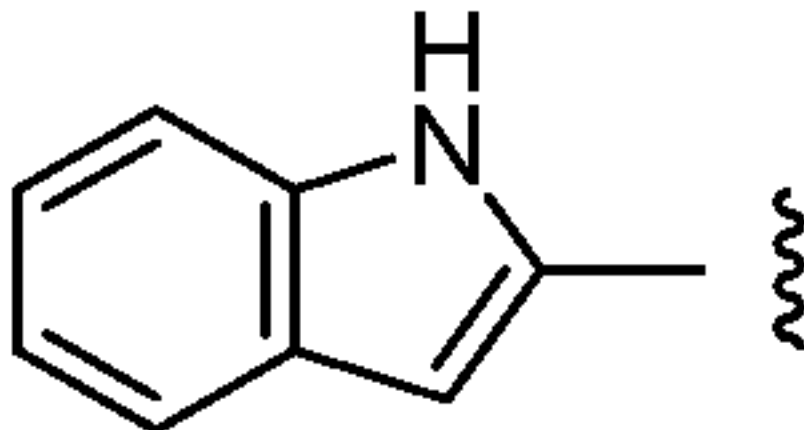
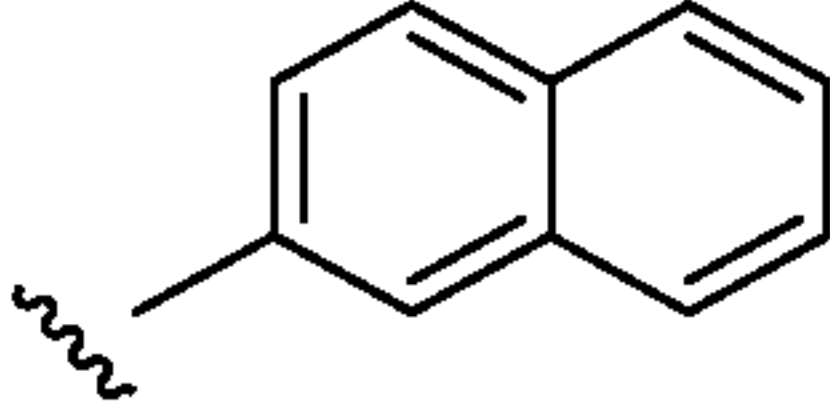
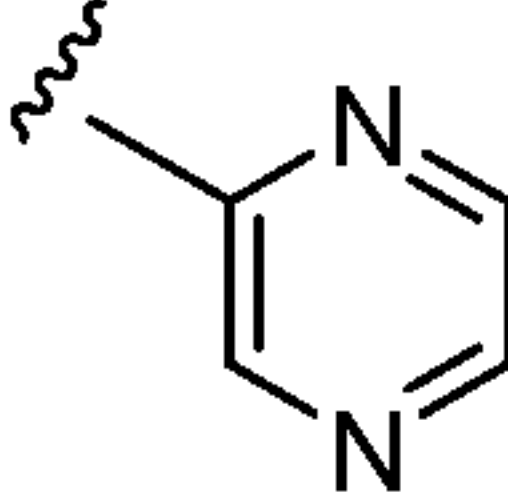
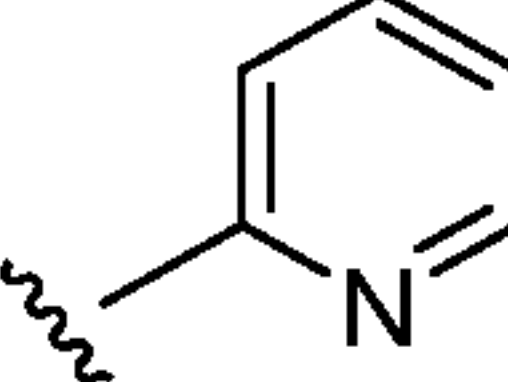
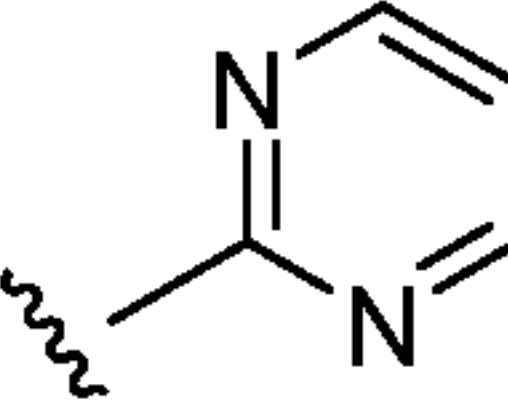
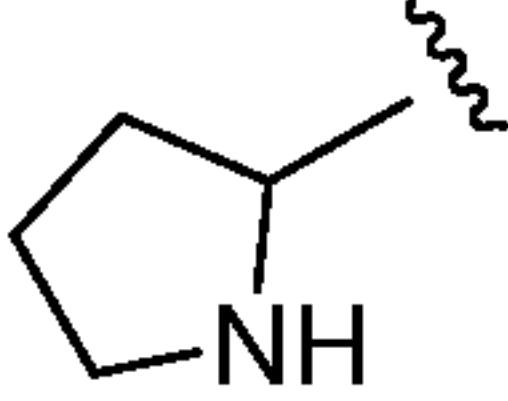
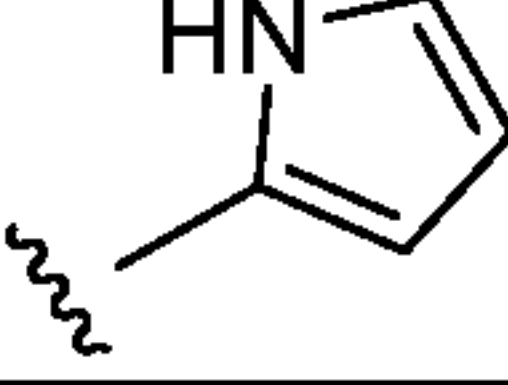
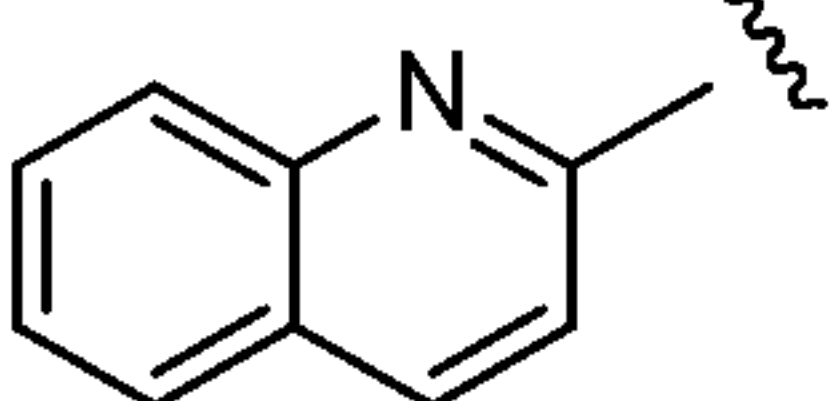
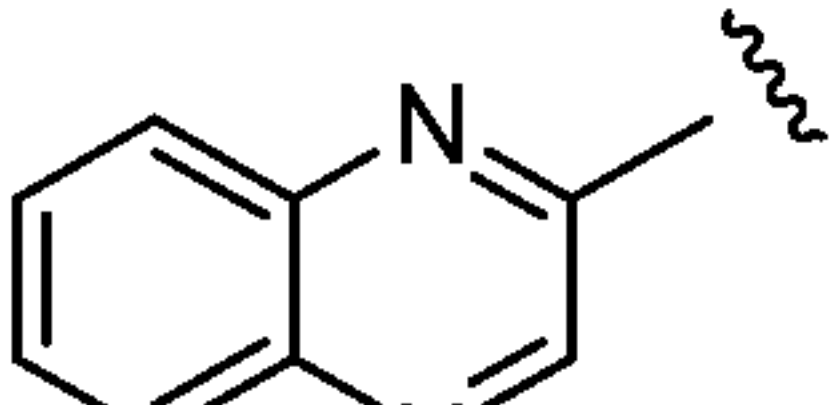
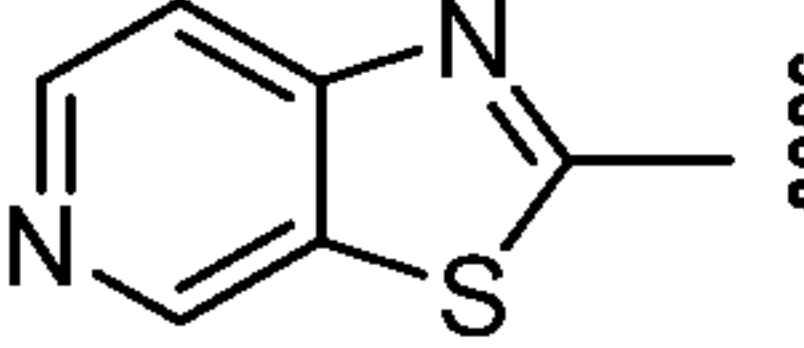
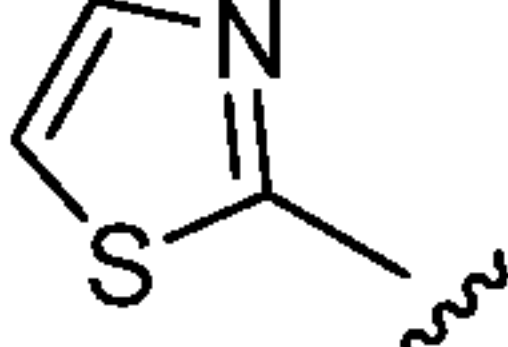
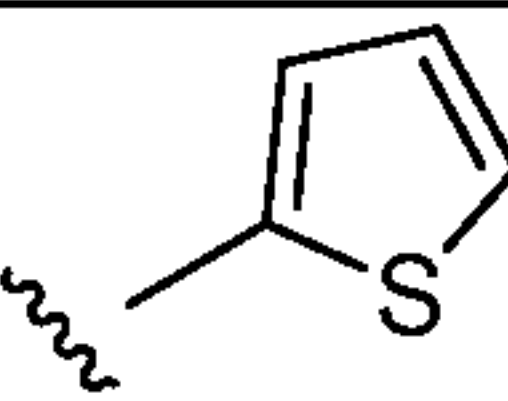
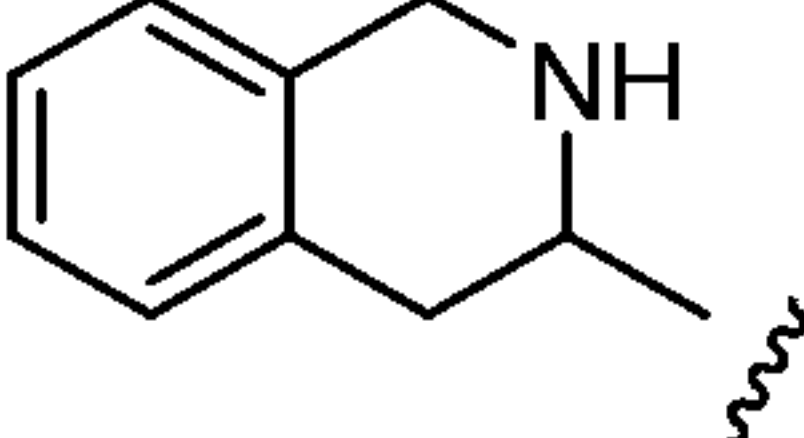
Definitions

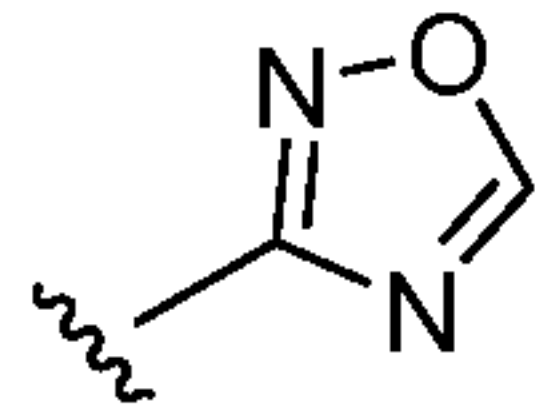
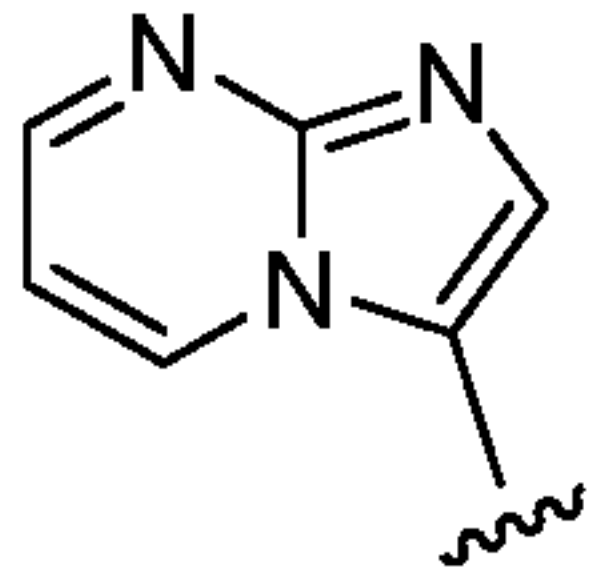
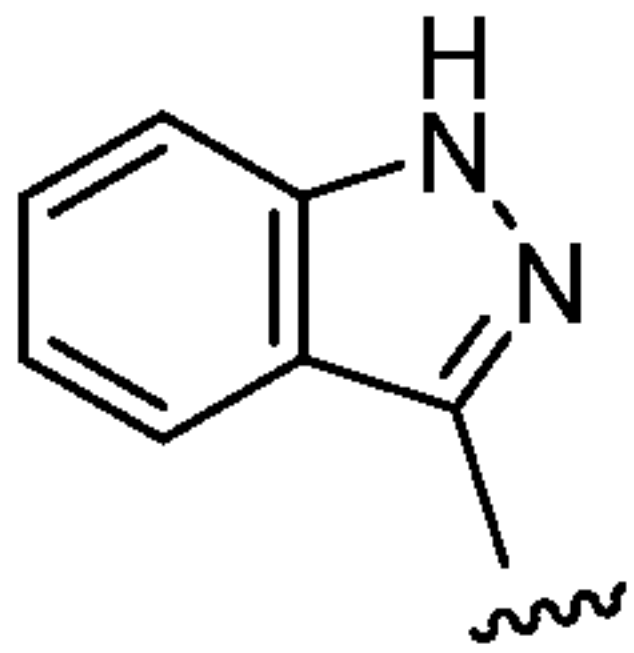
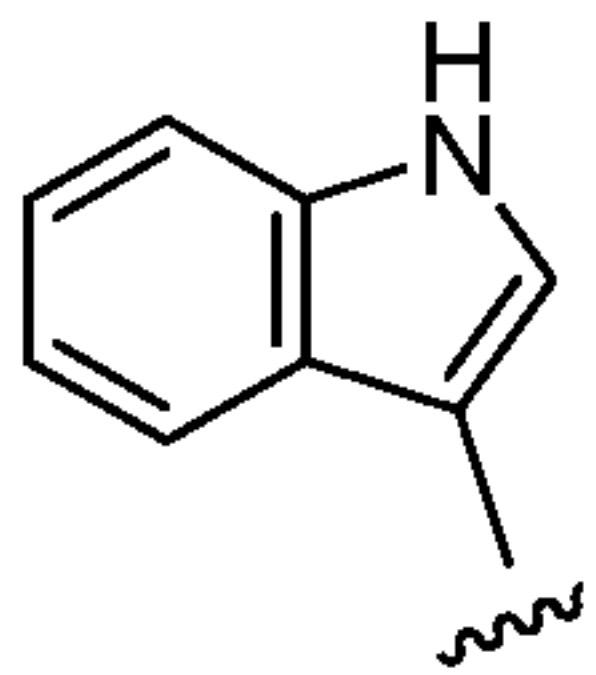
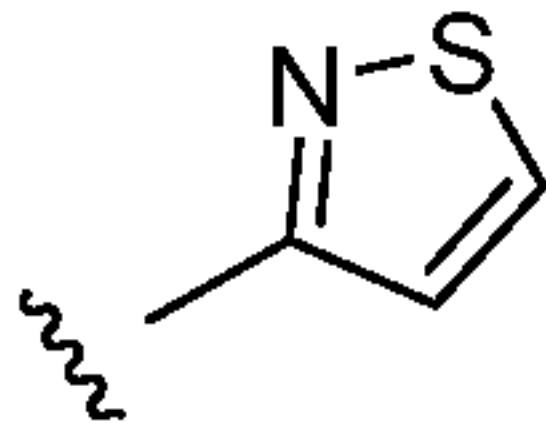
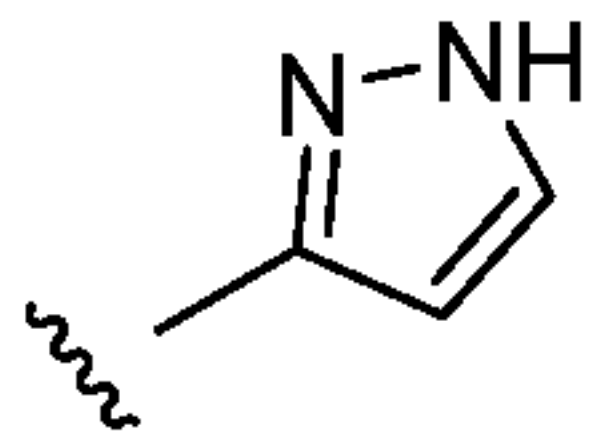
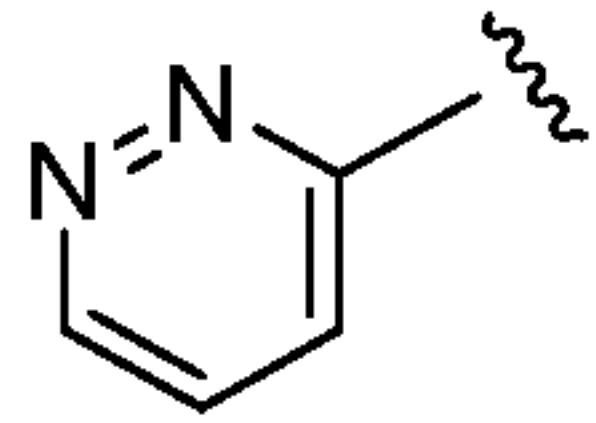
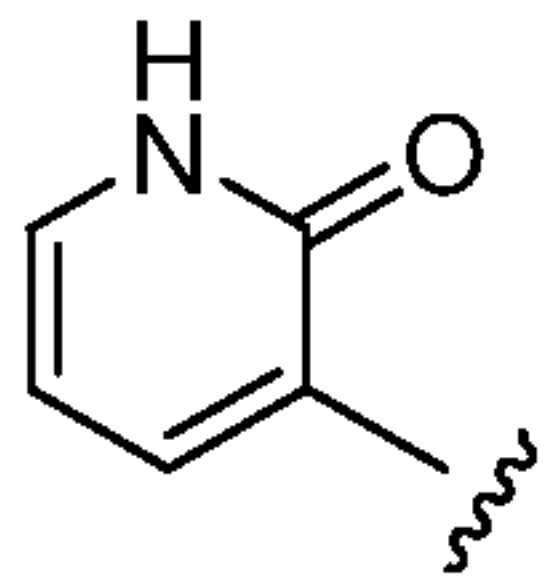
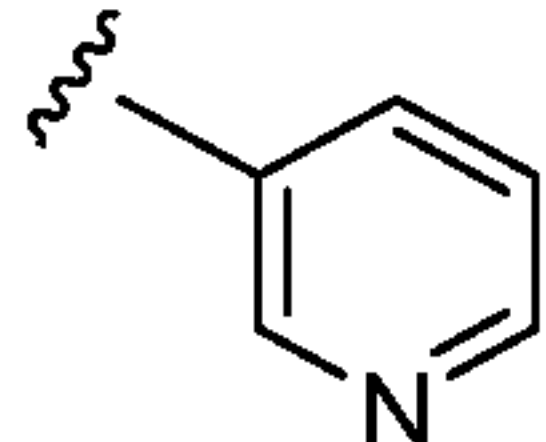
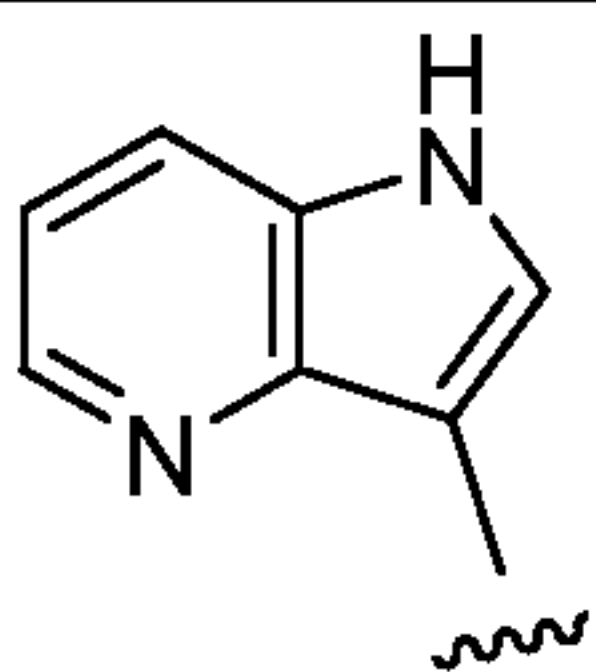
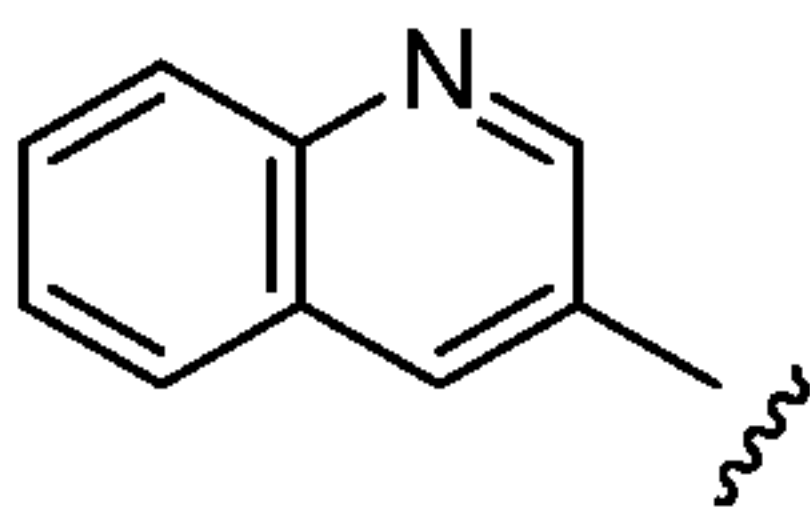
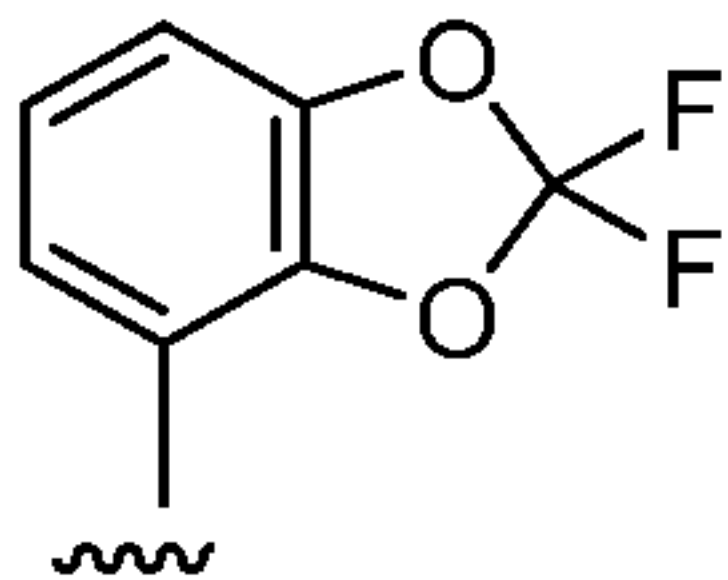
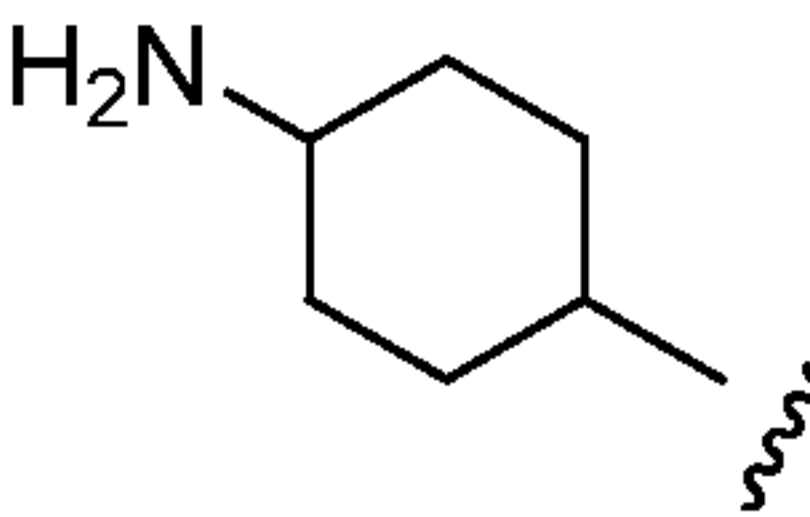
[0107] For the purpose of the present disclosure, the terms used in connection with A or A¹ have the chemical structures set forth in Table 2, each of which may be optionally

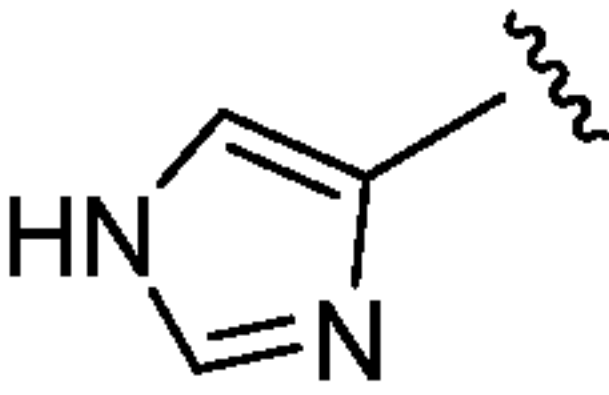
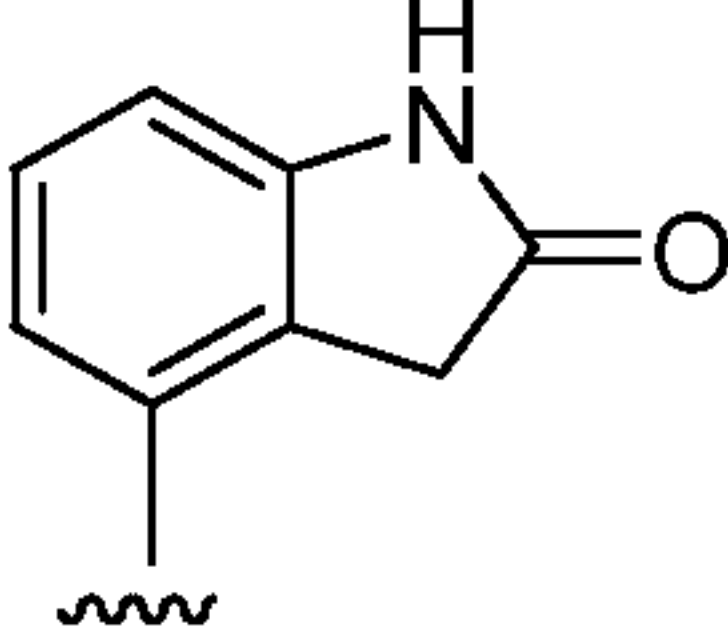
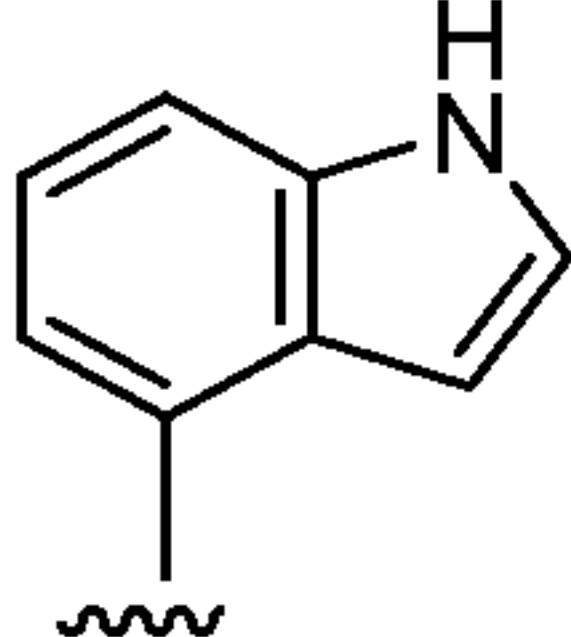
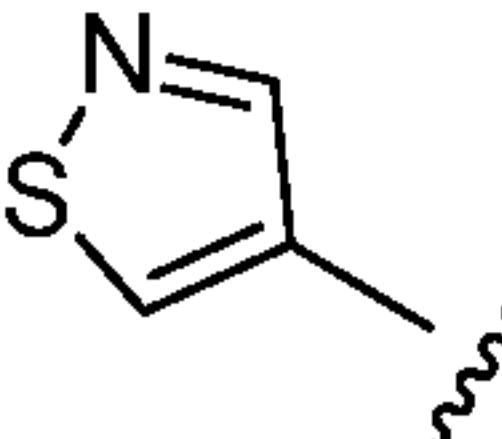
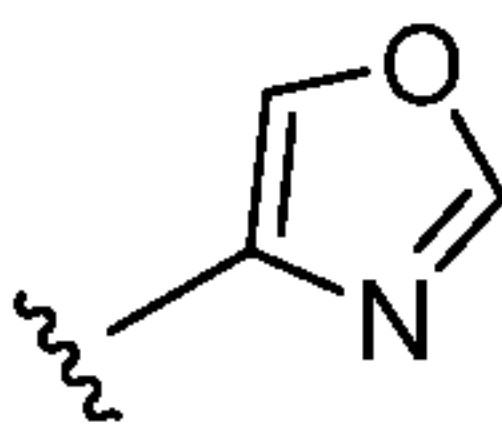
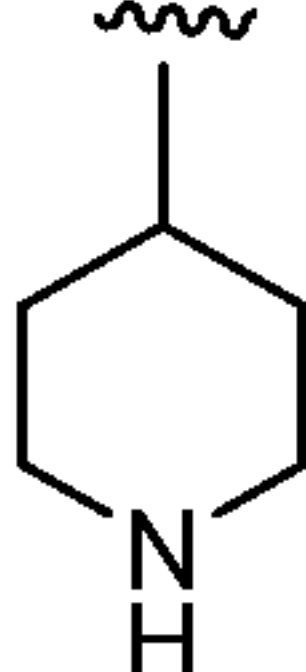
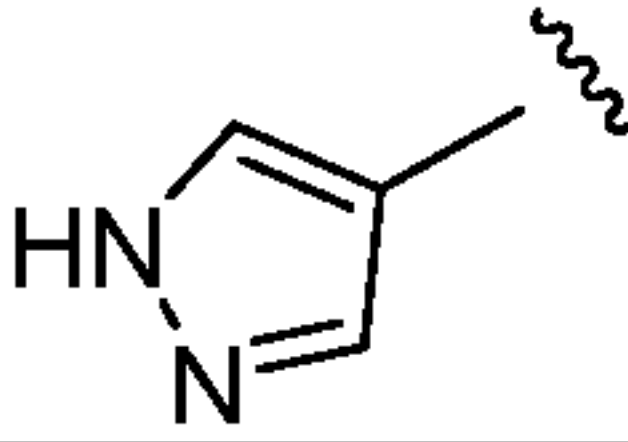
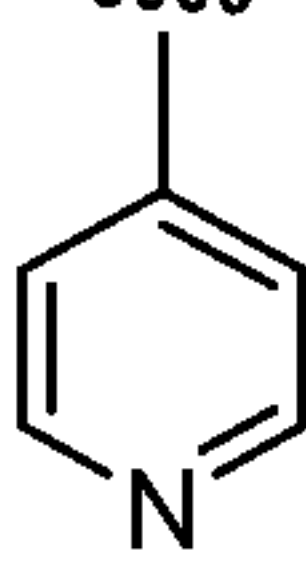
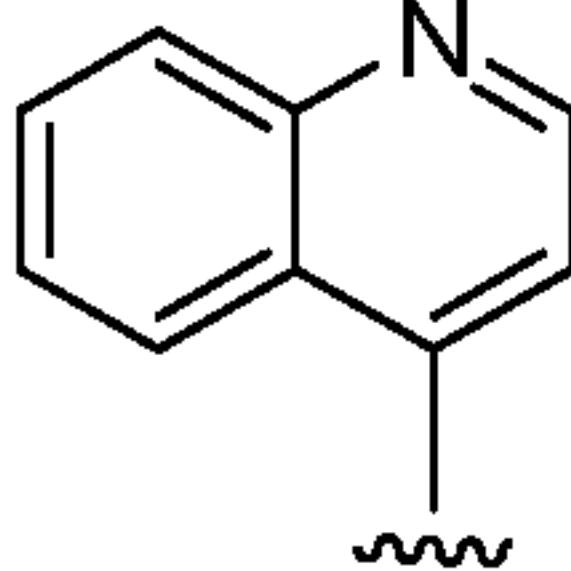
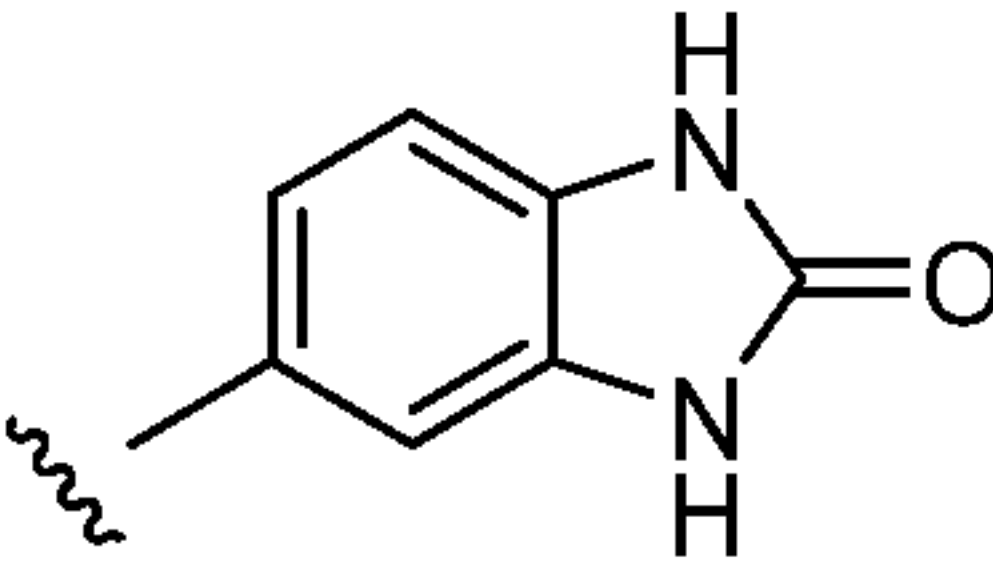
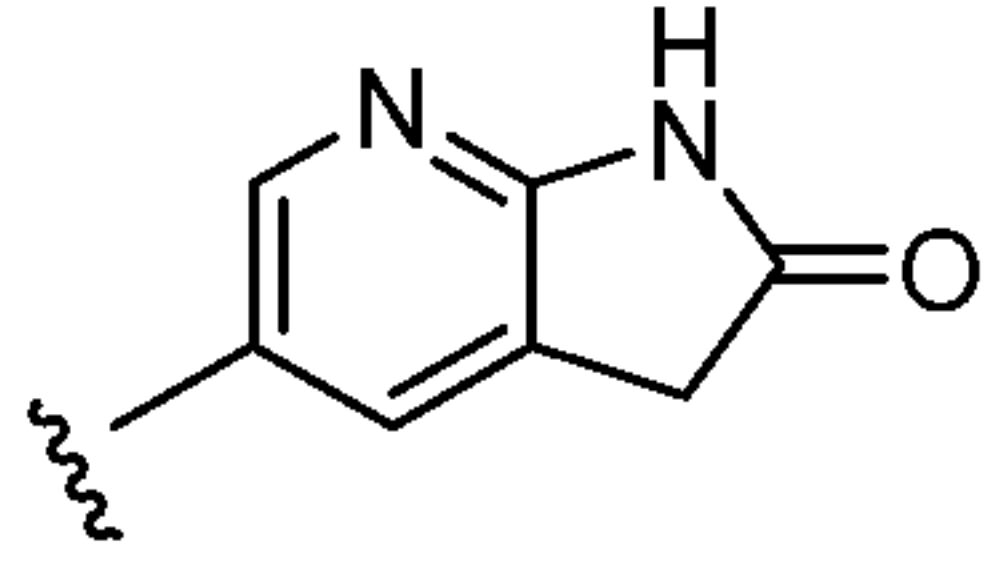
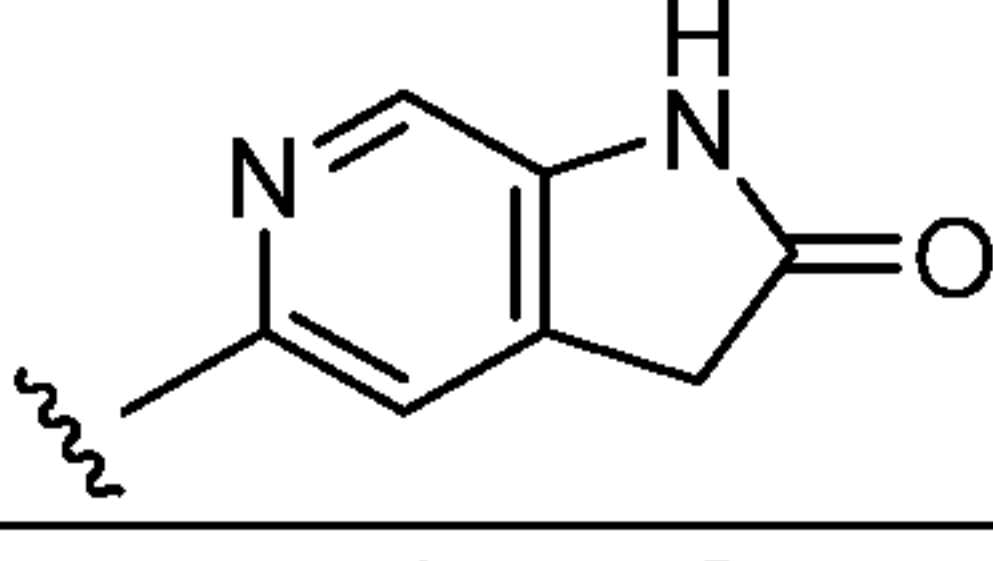
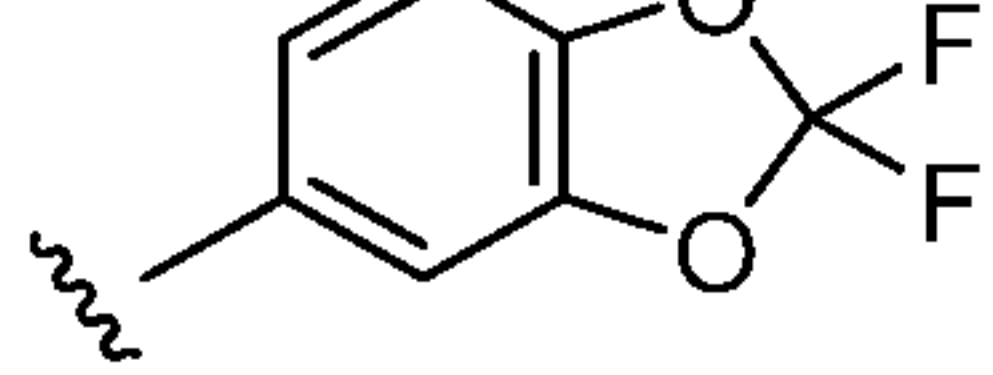
substituted with one or more substituents, *e.g.*, 1, 2, 3, 4, or 5 substituents, depending on the nature of the group and the number of available positions. For example, when A or A¹ is 2-furanyl there are three carbon atoms for available for substitution. When A or A¹ is 2-naphthalenyl there are seven carbon atoms available for substitution. Substitution may occur at any available carbon or nitrogen atom. Optional substituents include, but are not limited to, halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, C₁₋₆ alkyl, haloalkyl, hydroxyalkyl, (carboxamido)alkyl, (cycloalkyl)alkyl, optionally substituted C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 5- to 14-membered heteroaryl, optionally substituted 4- to 14-membered heterocyclo, or aralkyl.

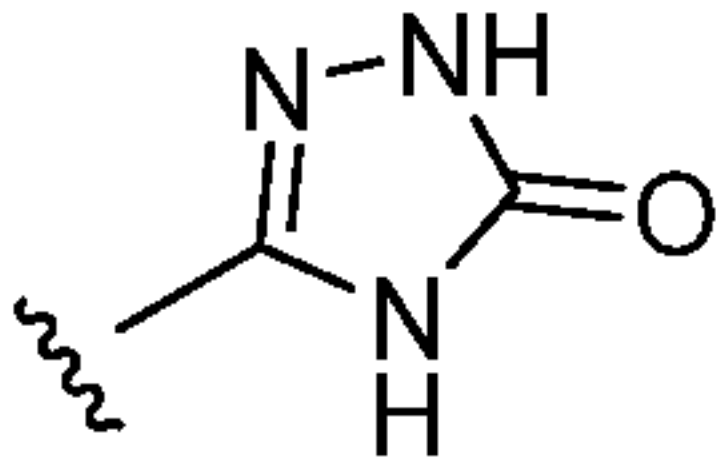
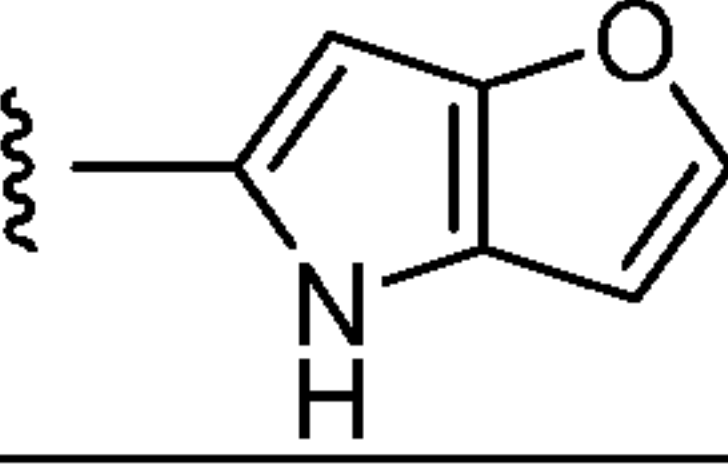
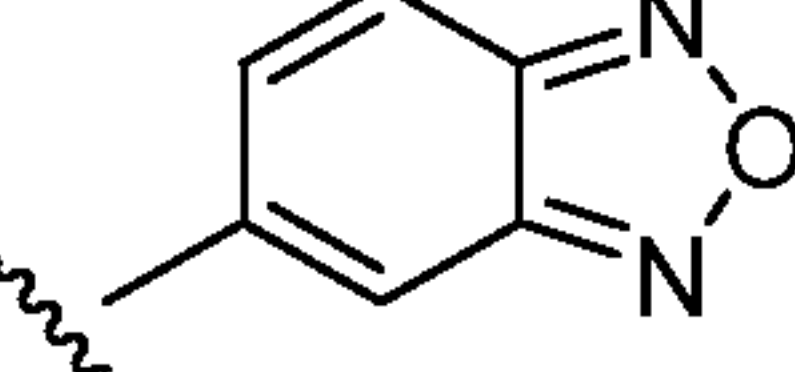
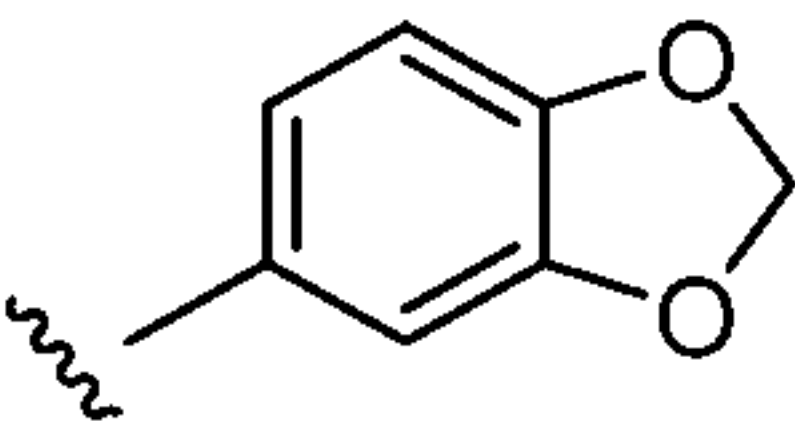
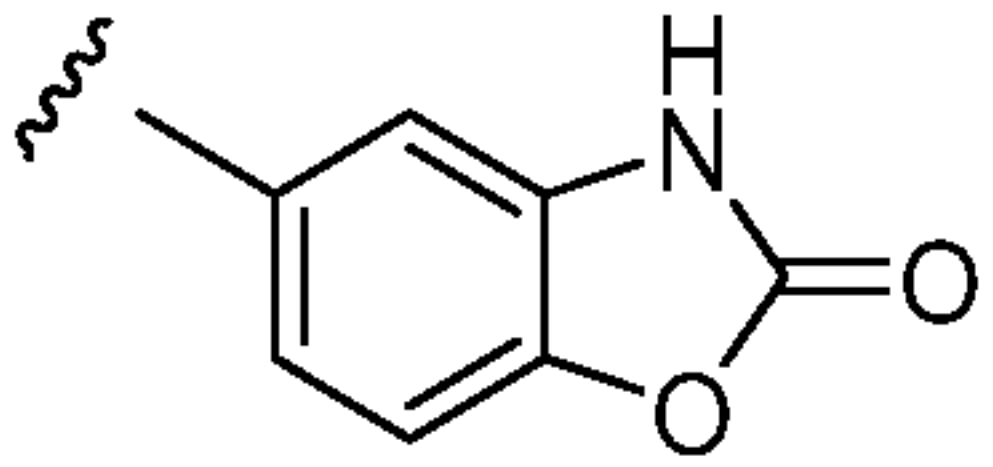
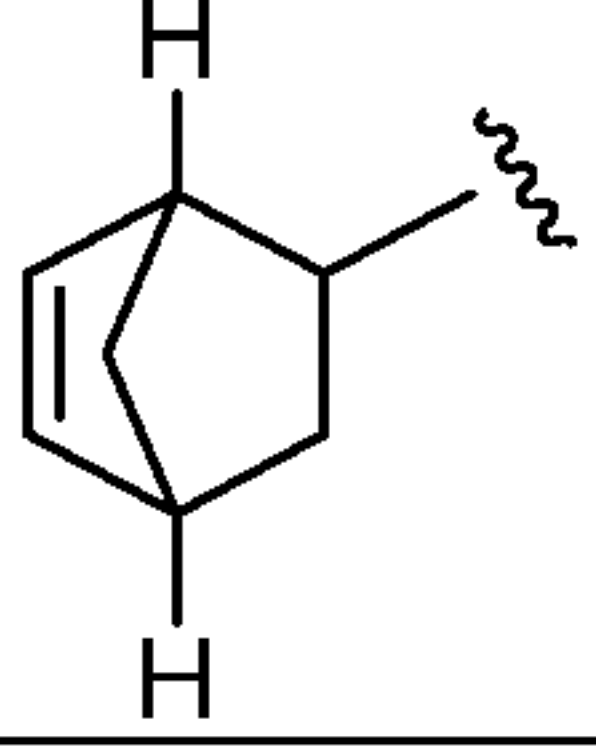
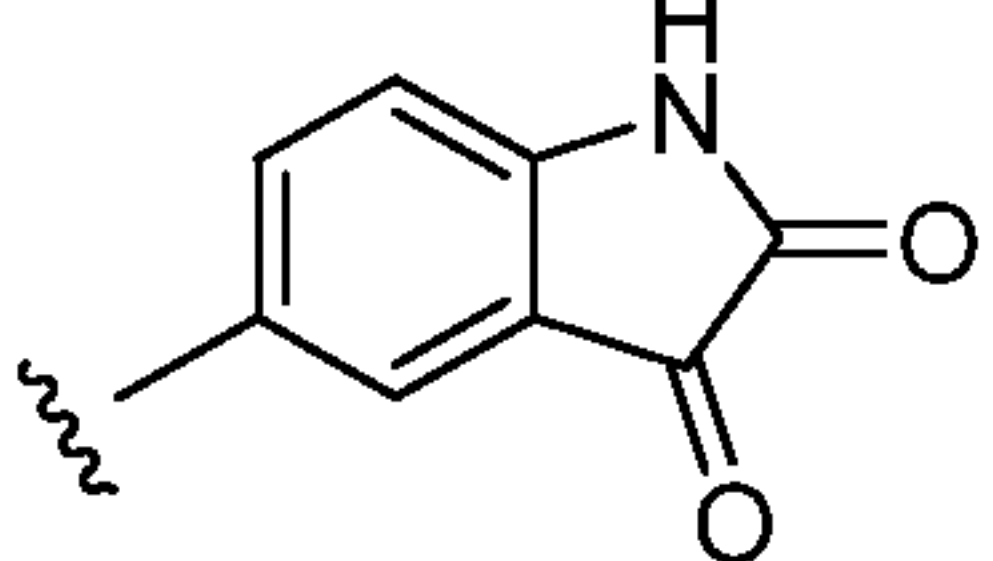
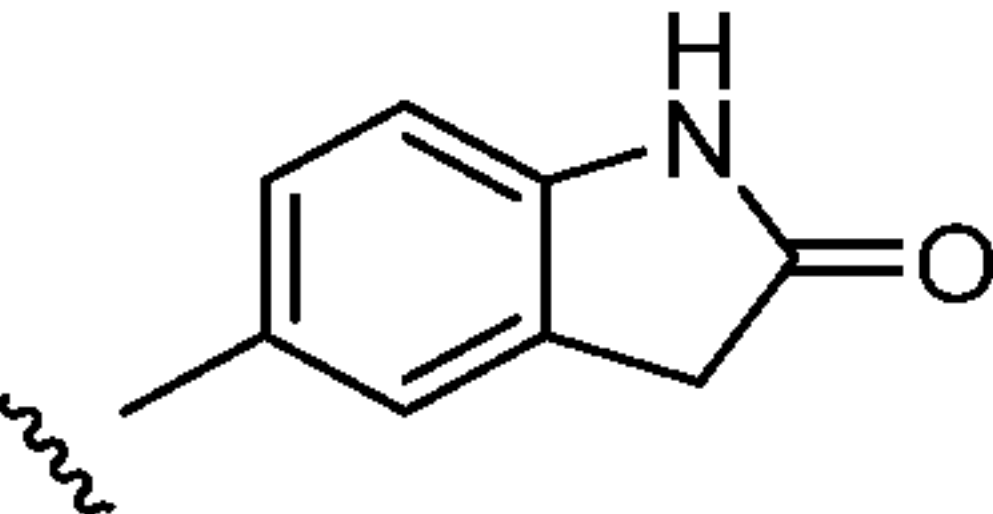
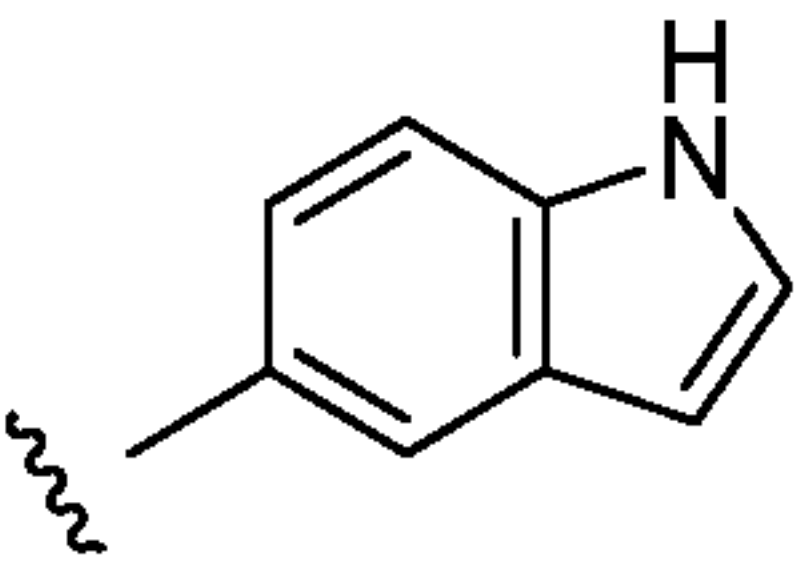
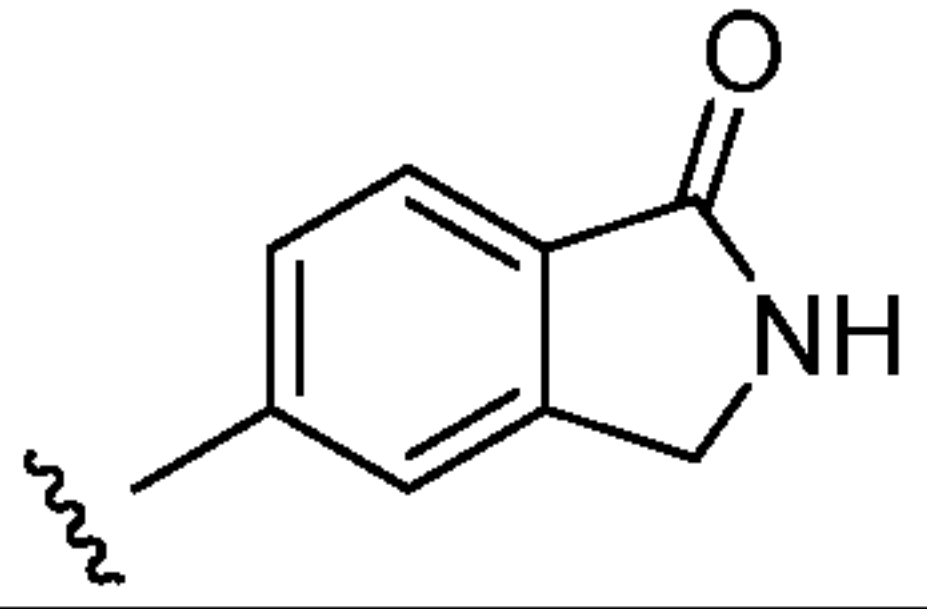
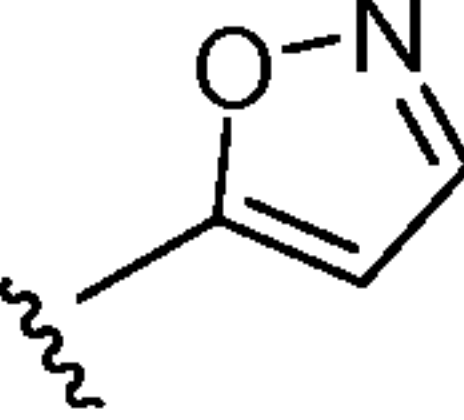
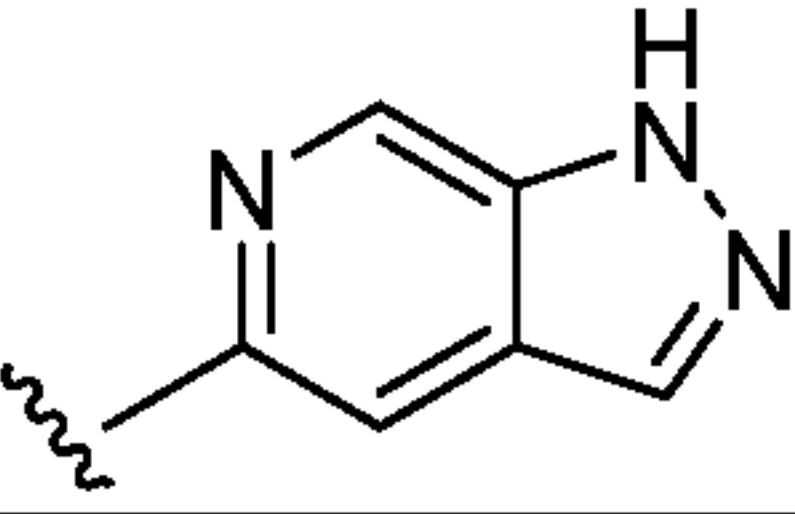
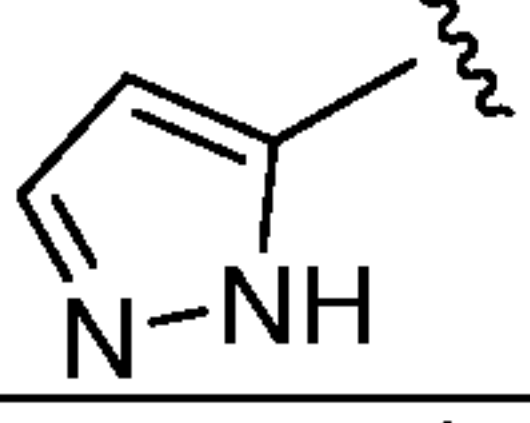
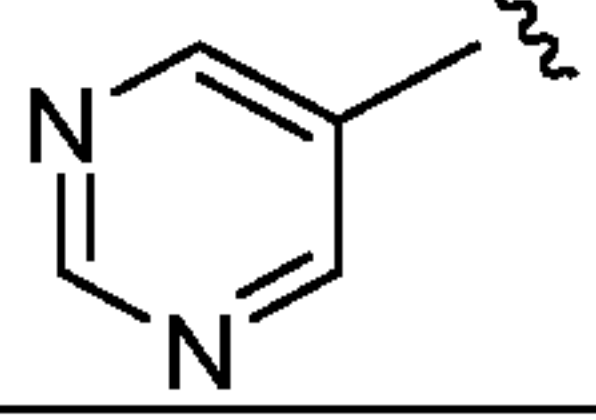
Table 2

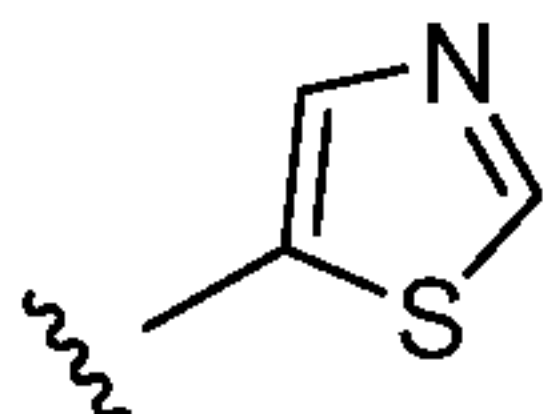
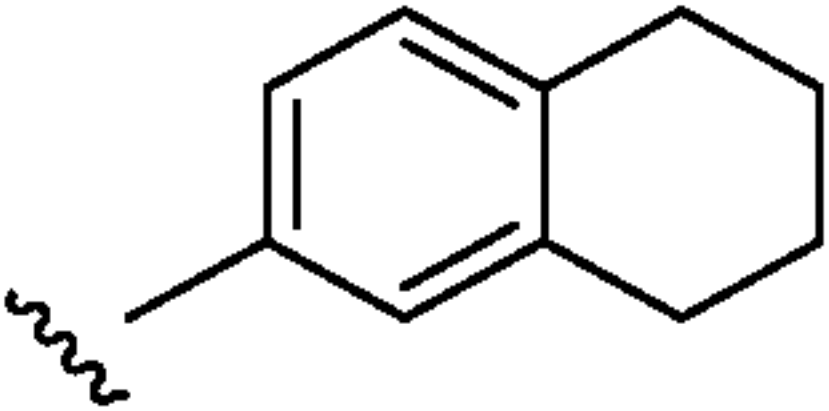
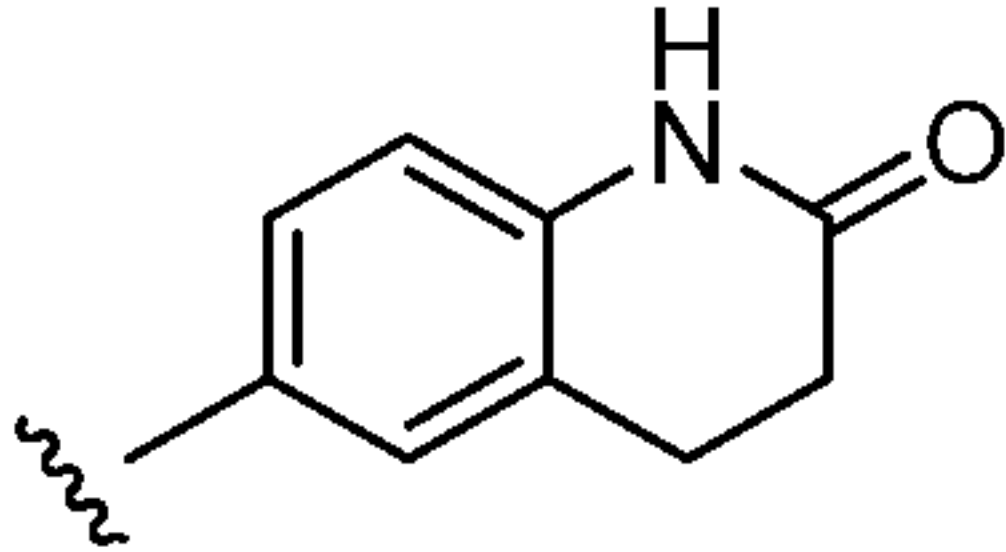
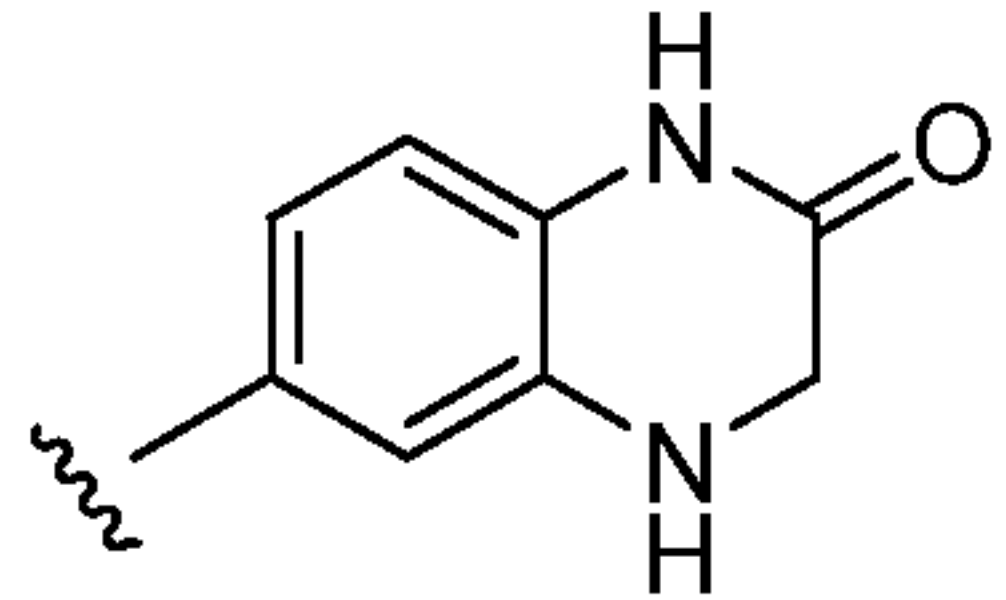
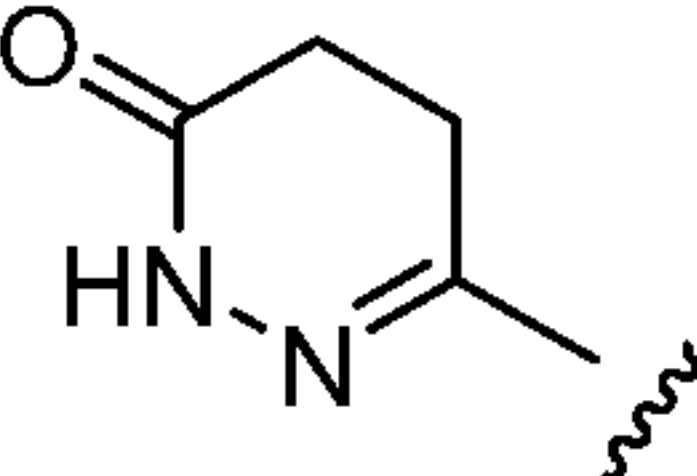
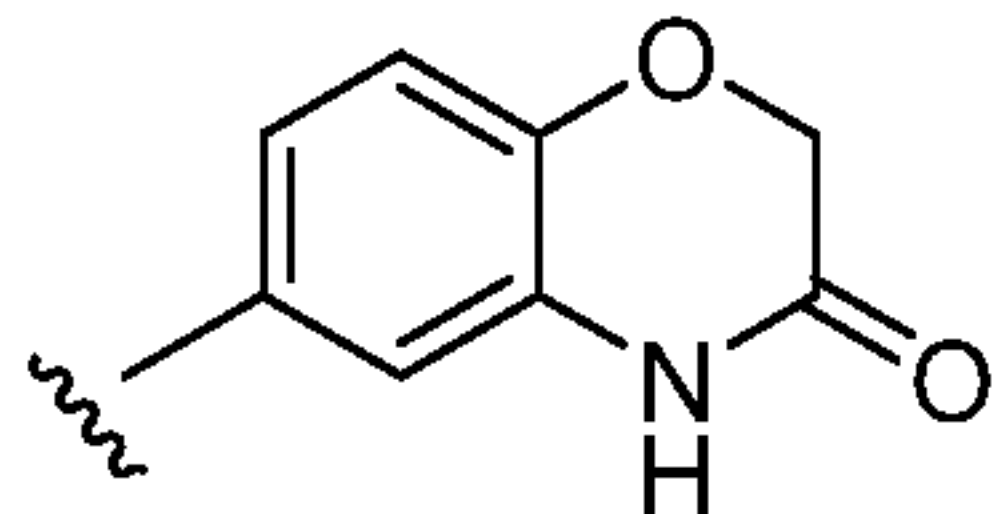
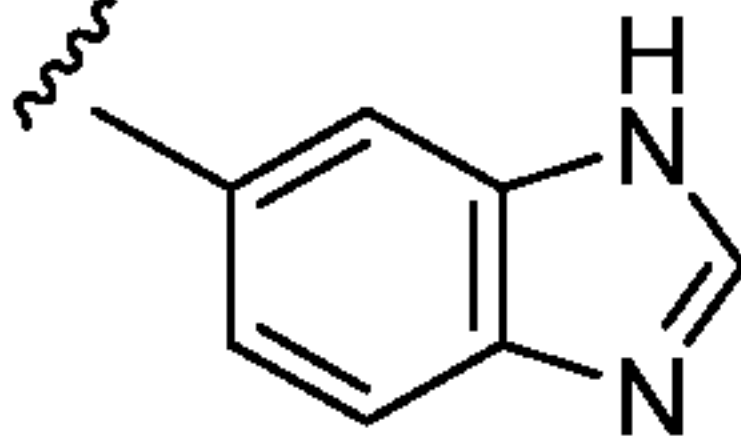
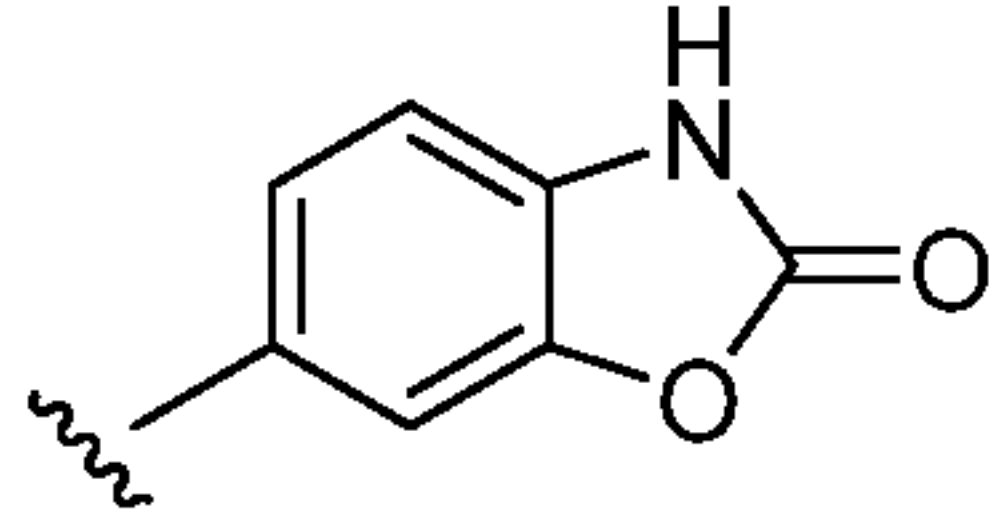
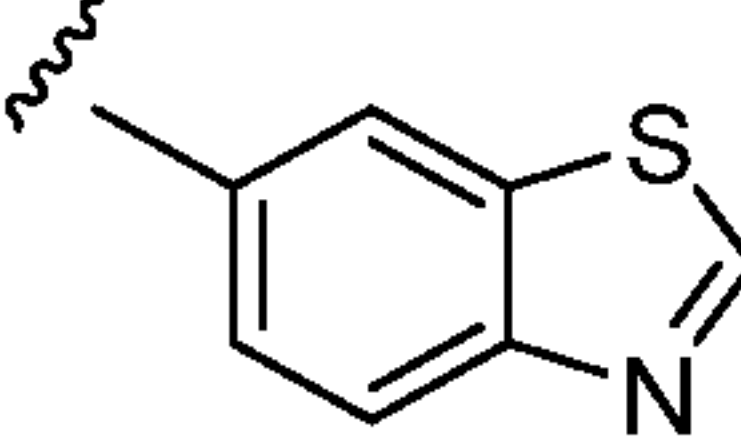
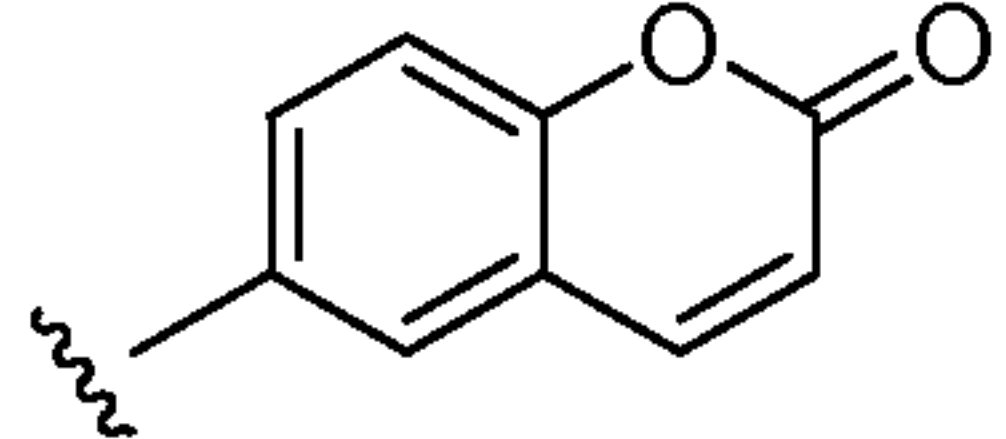
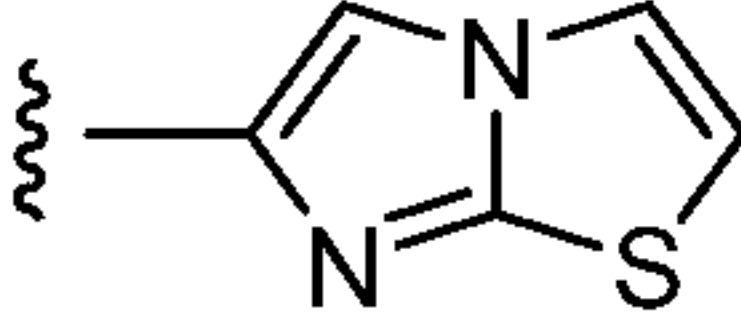
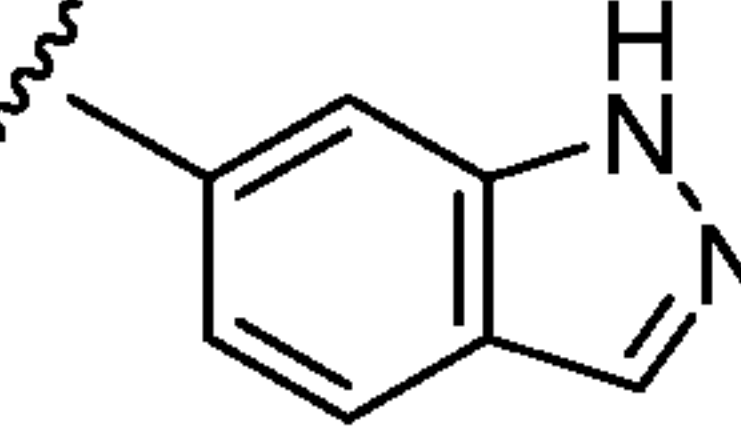
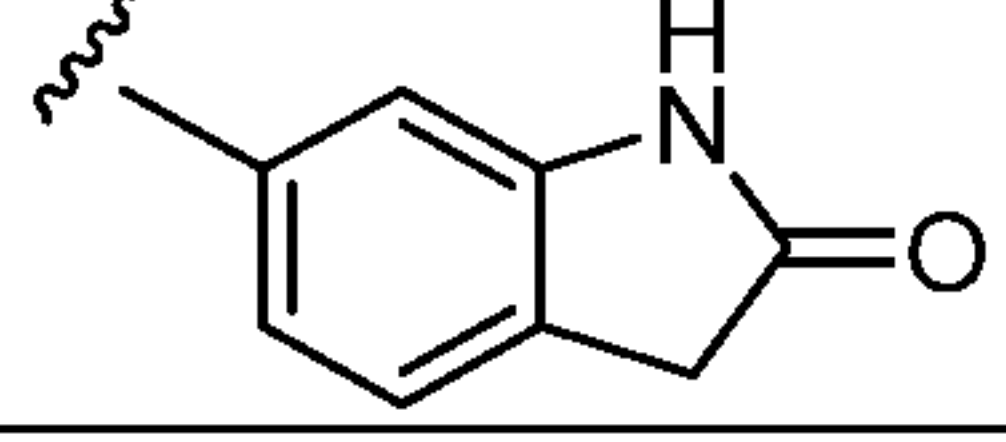
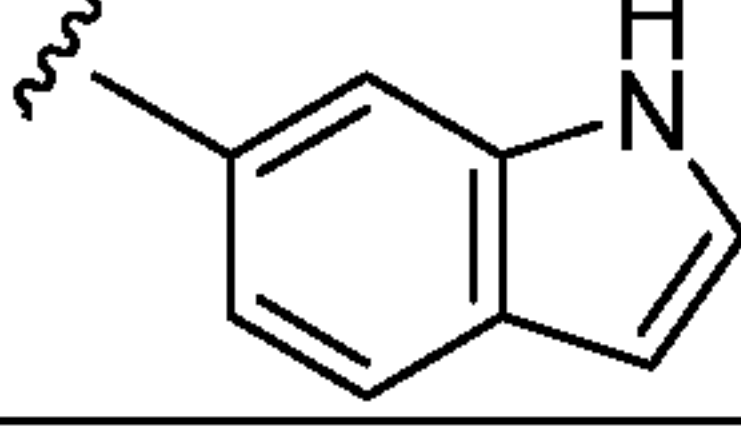
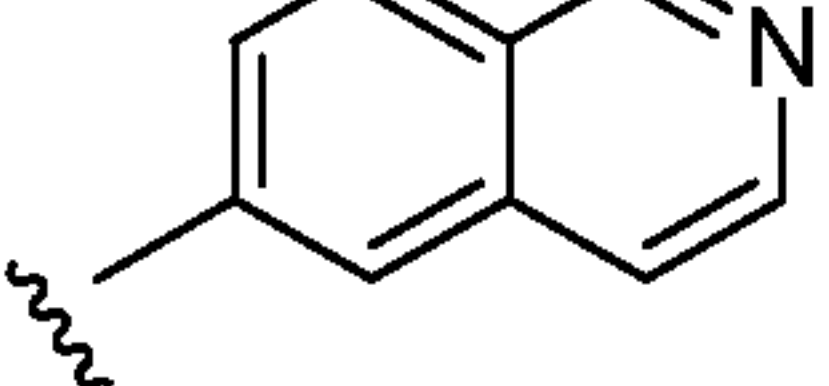
A or A ¹	Chemical structure
1,2,3-triazolyl	
1,2,4-triazolyl	
1-imidazolyl	
1-isoquinolinyl	
1-pyrazolyl	
2-(1,2,3,4-tetrahydroquinolinyl)	
2-benzo[d]imidazolyl	
2-benzo[d]thiazolyl	
2-chromenyl-4-one	

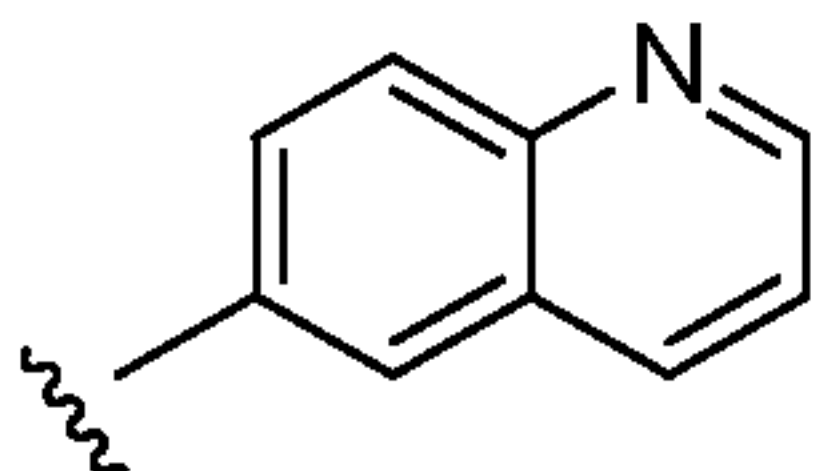
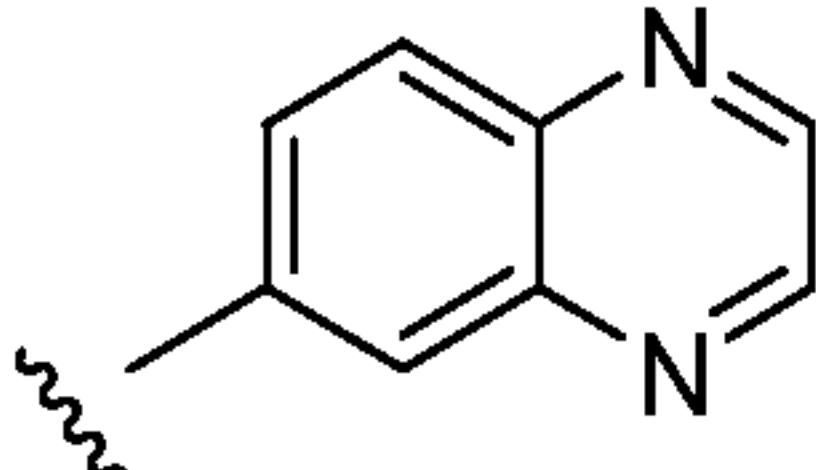
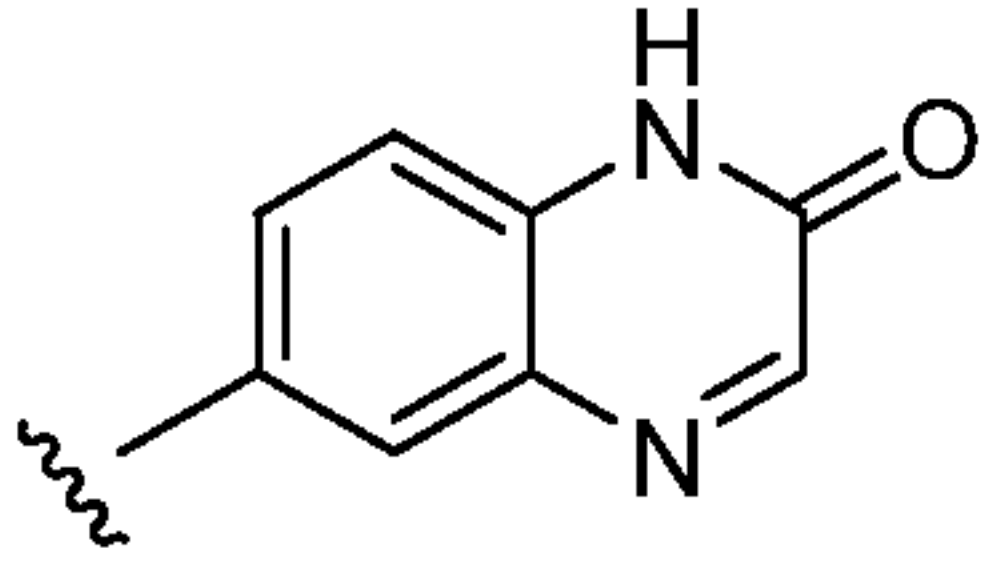
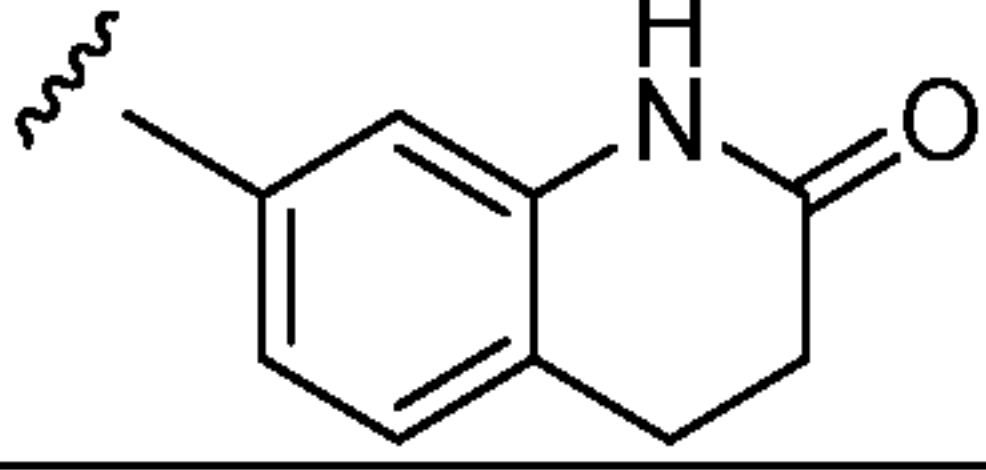
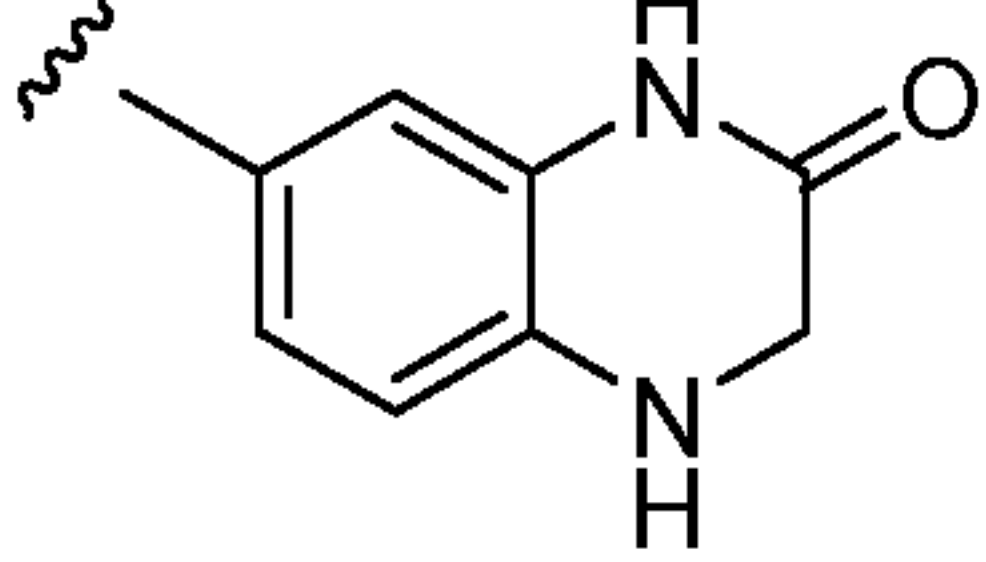
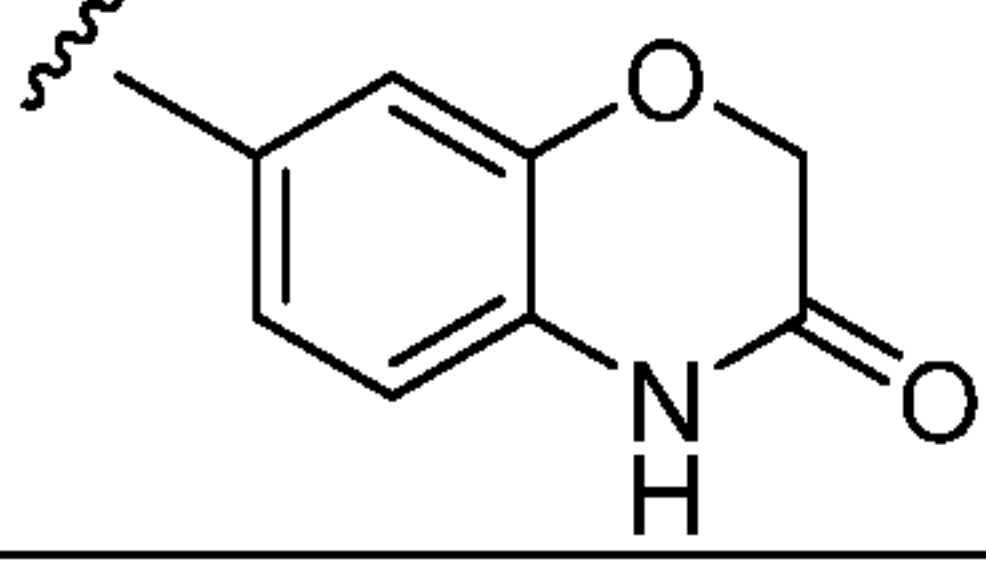
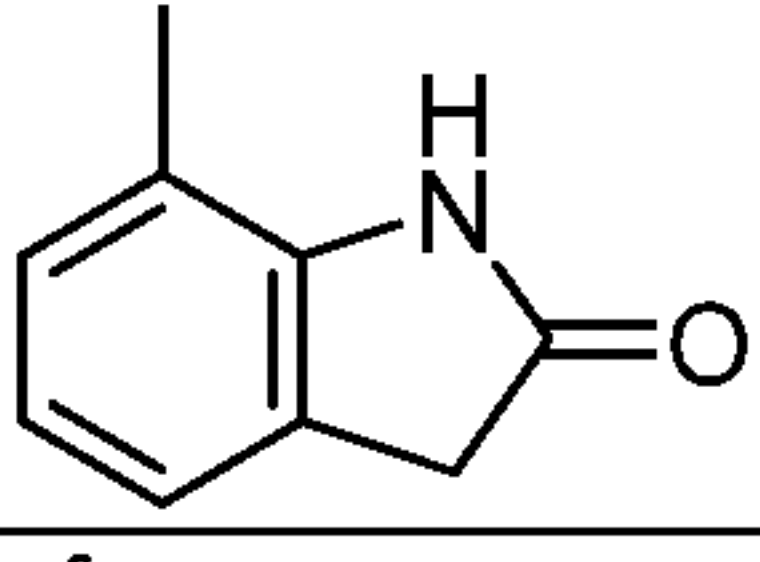
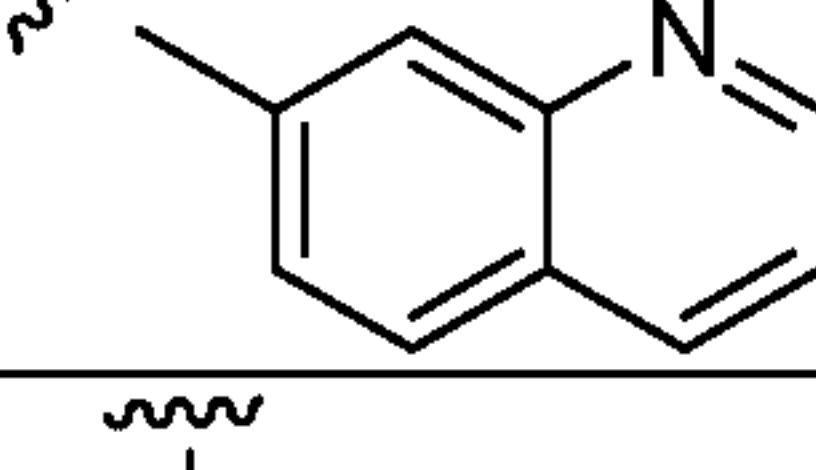
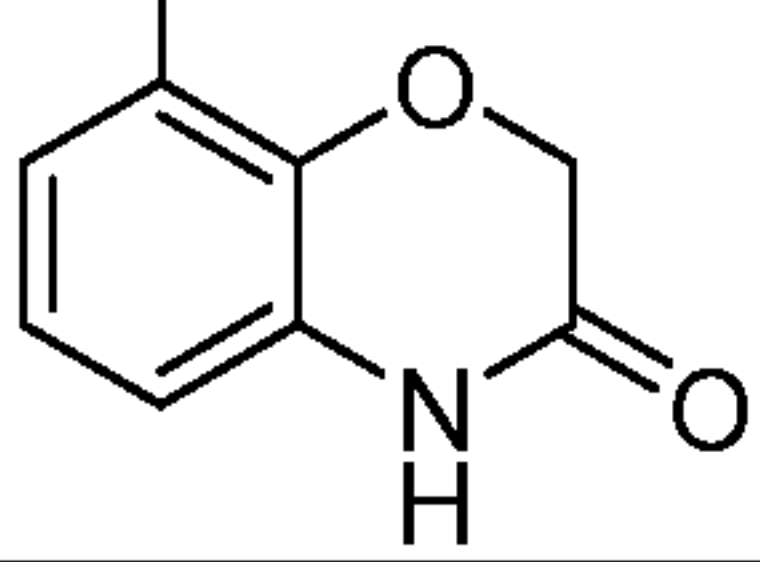
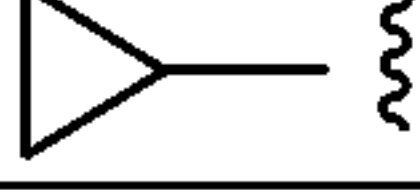
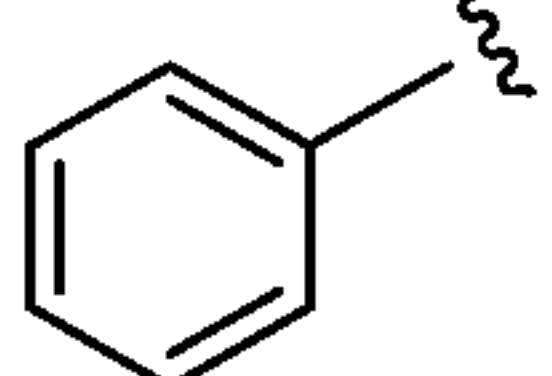
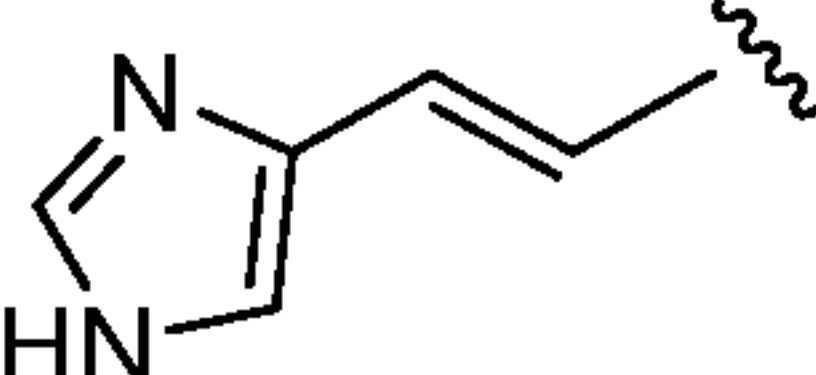
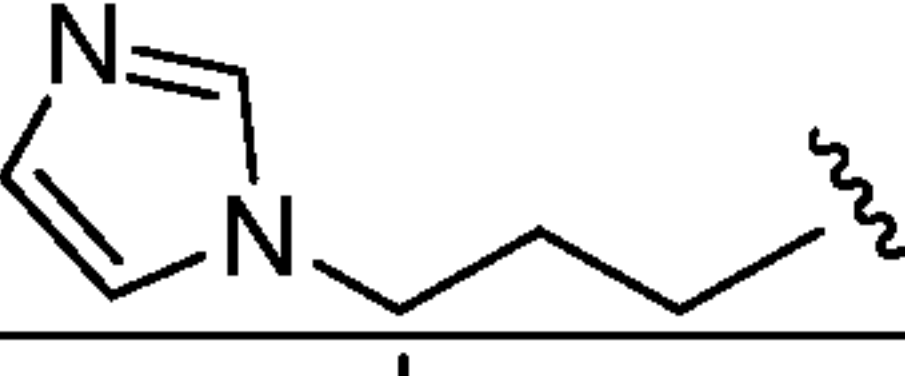
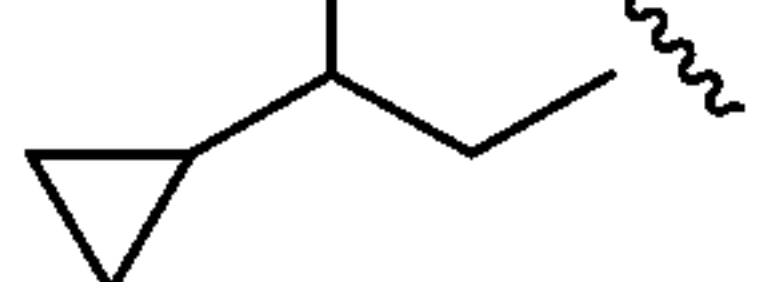
2-furanyl	
2-imidazo[1,2-b]pyridazinyl	
2-imidazolyl	
2-indolyl	
2-naphthalenyl	
2-pyrazinyl	
2-pyridyl	
2-pyrimidinyl	
2-pyrrolidinyl	
2-pyrrolyl	
2-quinolinyl	
2-quinoxaliny	
2-thiazolo[5,4-c]pyridinyl	
2-thiazolyl	
2-thiophenyl	
3-(1,2,3,4-tetrahydroisoquinoline)	

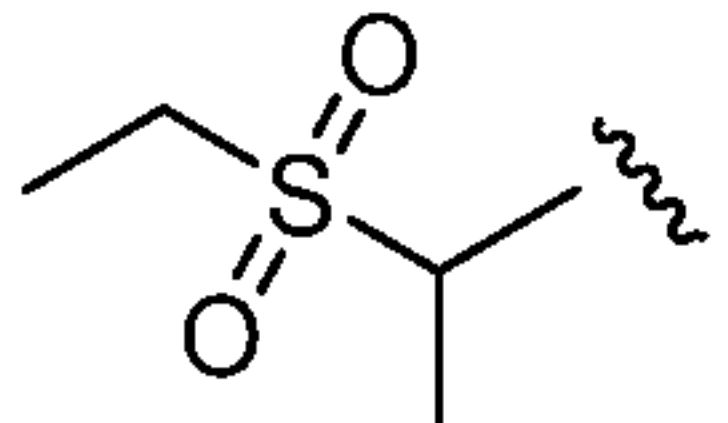
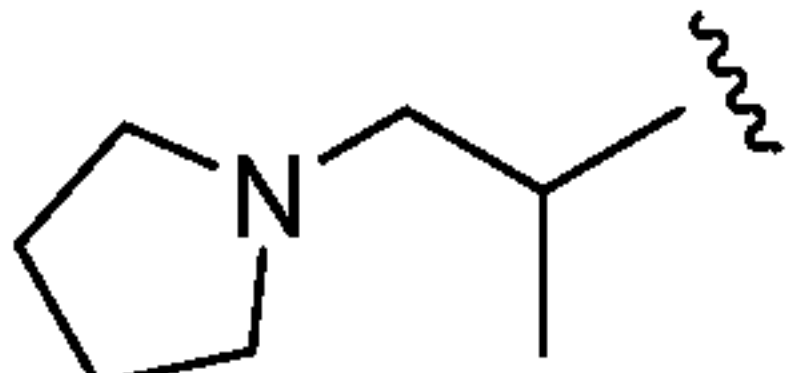
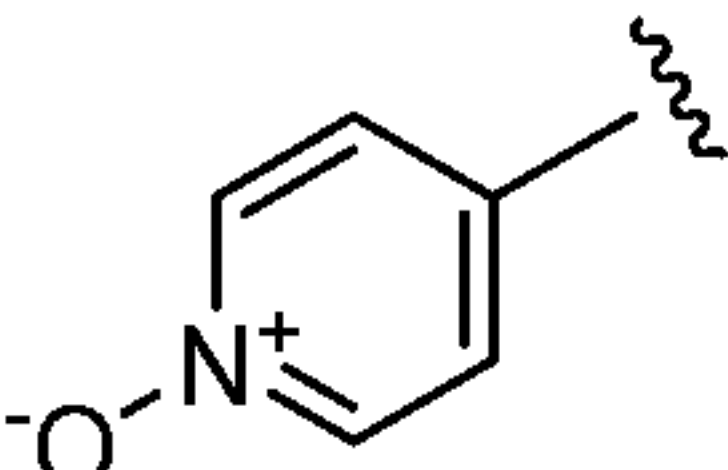
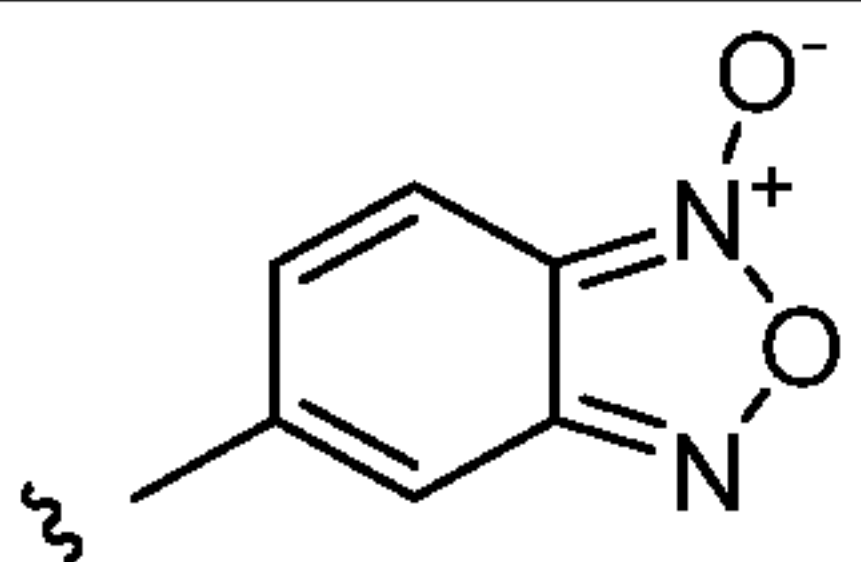
3-(1,2,4-oxadiazolyl)	
3-imidazo[1,2-a]pyrimidinyl	
3-indazolyl	
3-indolyl	
3-isothiazolyl	
3-pyrazolyl	
3-pyridazinyl	
3-pyridinyl-2-one	
3-pyridyl	
3-pyrrolo[3,2-b]pyridinyl	
3-quinolinyl	
4-(2,2-difluorobenzo[d][1,3]dioxolyl)	
4-cyclohexanyl-1-amine	

4-imidazolyl	
4-indolinyl-2-one	
4-indolyl	
4-isothiazolyl	
4-oxazolyl	
4-piperidiny	
4-pyrazolyl	
4-pyridyl	
4-quinoliny	
5-(1,3-dihydro-2H-benzo[d]imidazolyl-2-one)	
5-(1,3-dihydro-2H-pyrrolo[2,3-b]pyridinyl-2-one)	
5-(1,3-dihydro-2H-pyrrolo[2,3-c]pyridinyl-2-one)	
5-(2,2-difluorobenzo[d][1,3]dioxolyl)	

5-(2,4-dihydro-3H-1,2,4-triazolyl-3-one)	
5-4H-furo[3,2-b]pyrrolyl	
5-benzo[c][1,2,5]oxadiazolyl	
5-benzo[d][1,3]dioxolyl	
5-benzo[d]oxazolyl-2(3H)-one	
5-bicyclo[2.2.1]heptyl-2-ene	
5-indolinyl-2,3-dione	
5-indolinyl-2-one	
5-indolyl	
5-isoindolinyl-1-one	
5-isoxazolyl	
5-pyrazolo[3,4-c]pyridinyl	
5-pyrazolyl	
5-pyrimidinyl	

5-thiazolyl	
6-(1,2,3,4-tetrahydronaphthalenyl)	
6-(3,4-dihydroquinolinyl-2(1H)-one)	
6-(3,4-dihydroquinoxaliny-2(1H)-one)	
6-(4,5-dihydropyridazinyl-3(2H)-one)	
6-benzo[b][1,4]oxazinyl-3-one	
6-benzo[d]imidazolyl	
6-benzo[d]oxazolyl-2(3H)-one	
6-benzo[d]thiazolyl	
6-chromenyl-2-one	
6-imidazo[2,1-b]thiazole	
6-indazolyl	
6-indoliny-2-one	
6-indolyl	
6-isoquinoliny-2-one	

6-quinolinyl	
6-quinoxalyl	
6-quinoxalyl-2(1H)-one	
7-(3,4-dihydroquinolinyl-2(1H)-one)	
7-(3,4-dihydroquinoxalin-2(1H)-one)	
7-benzo[b][1,4]oxazinyl-3-one	
7-indolinyl-2-one	
7-quinolinyl	
8-benzo[b][1,4]oxazinyl-3-one	
cyclopropanyl	
phenyl	
4-(prop-1-en-1-yl)-imidazole	
1-butanyl-imidazole	
sec-butylcyclopropane	

2-(ethylsulfonyl)propanyl	
1-isobutylpyrrolidine	
4-pyridyl 1-oxide	
5-benzo[c][1,2,5]oxadiazolyl 1-oxide	

[0108] For the purpose of the present disclosure, the term "alkyl" as used by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon containing one to twelve carbon atoms (*i.e.*, C₁₋₁₂ alkyl) or the number of carbon atoms designated (*i.e.*, a C₁ alkyl such as methyl, a C₂ alkyl such as ethyl, a C₃ alkyl such as propyl or isopropyl, etc.). In one embodiment, the alkyl group is chosen from a straight chain C₁₋₁₀ alkyl group. In another embodiment, the alkyl group is chosen from a branched chain C₃₋₁₀ alkyl group. In another embodiment, the alkyl group is chosen from a straight chain C₁₋₆ alkyl group. In another embodiment, the alkyl group is chosen from a branched chain C₃₋₆ alkyl group. In another embodiment, the alkyl group is chosen from a straight chain C₁₋₄ alkyl group. In another embodiment, the alkyl group is chosen from a branched chain C₃₋₄ alkyl group. In another embodiment, the alkyl group is chosen from a straight or branched chain C₃₋₄ alkyl group. In another embodiment, the alkyl group is partially or completely deuterated, *i.e.*, one or more hydrogen atoms of the alkyl group are replaced with deuterium atoms. Non-limiting exemplary C₁₋₁₀ alkyl groups include methyl (including -CD₃), ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, *iso*-butyl, 3-pentyl, hexyl, heptyl, octyl, nonyl, and decyl. Non-limiting exemplary C₁₋₄ alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, and *iso*-butyl.

[0109] For the purpose of the present disclosure, the term "optionally substituted alkyl" as used by itself or as part of another group means that the alkyl as defined above is either unsubstituted or substituted with one, two, or three substituents independently chosen from nitro, haloalkoxy, aryloxy, aralkyloxy, alkylthio, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy,

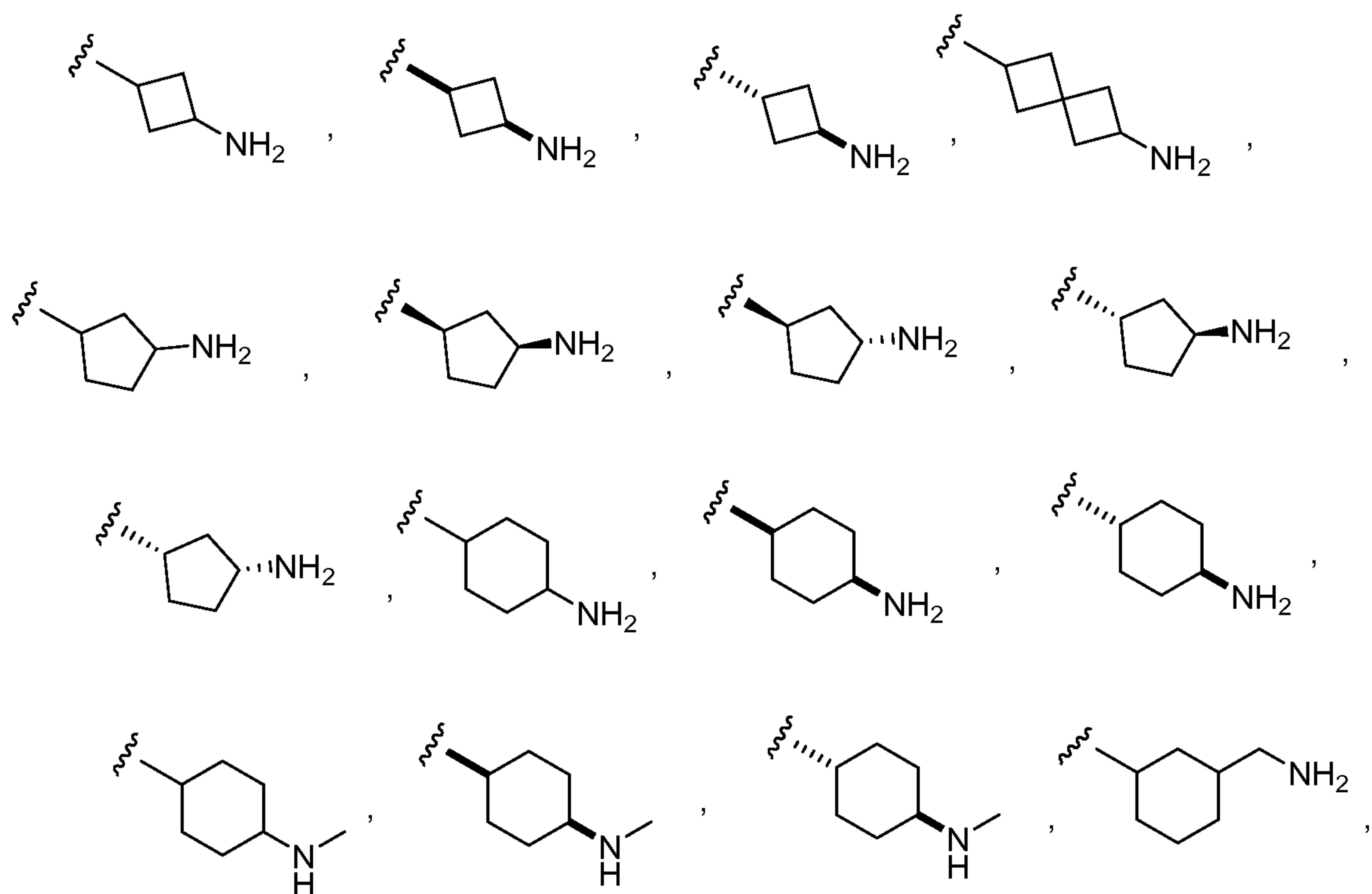
alkoxycarbonyl, and carboxyalkyl. In one embodiment, the alkyl is a C₁₋₆ alkyl. In another embodiment, the alkyl is a C₁₋₄ alkyl. In one embodiment, the optionally substituted alkyl is substituted with two substituents. In another embodiment, the optionally substituted alkyl is substituted with one substituent. Non-limiting exemplary optionally substituted alkyl groups include -CH₂CH₂NO₂, -CH₂CH₂CO₂H, -CH₂CH₂SO₂CH₃, -CH₂CH₂COPh, and -CH₂C₆H₁₁.

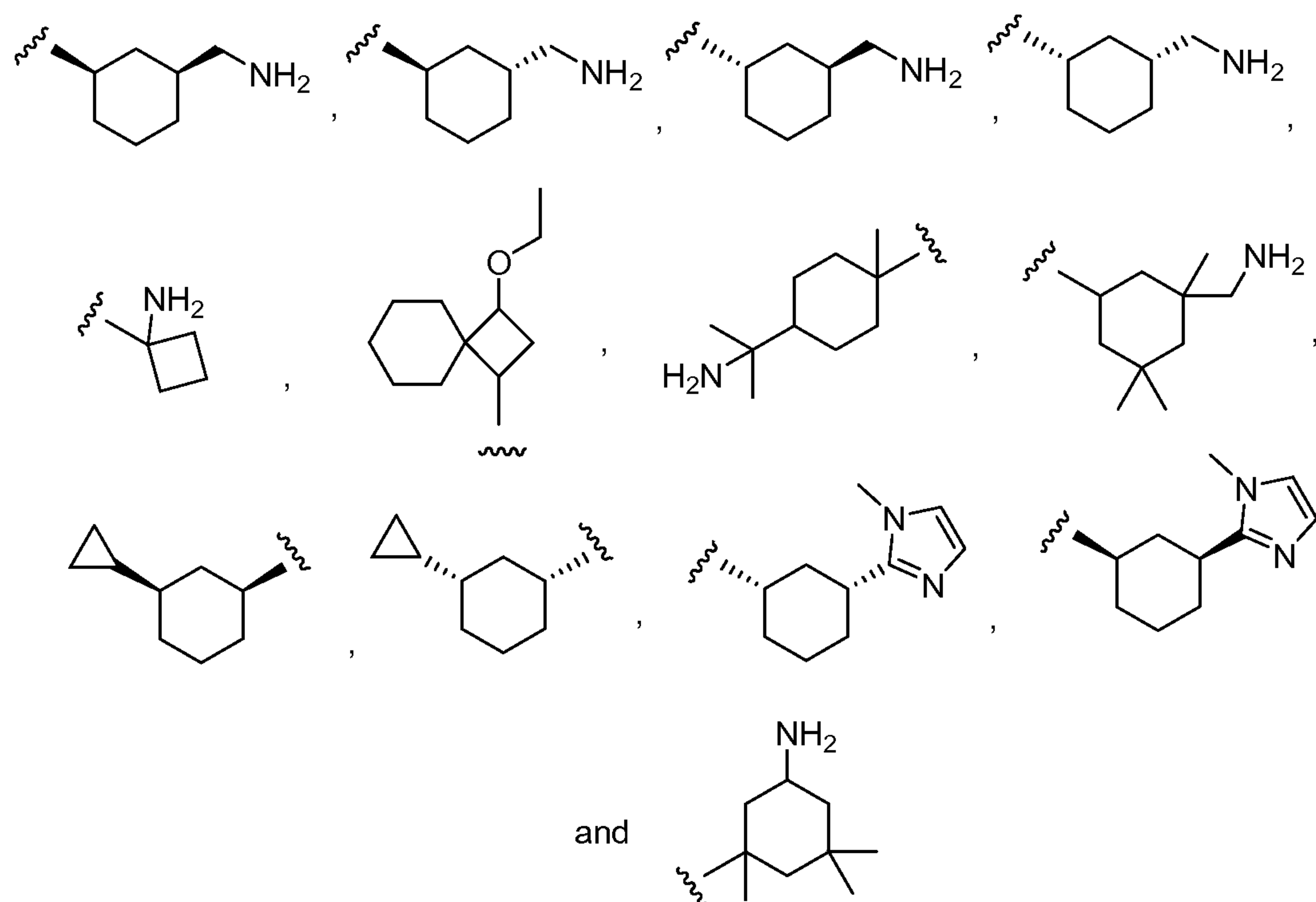
[0110] For the purpose of the present disclosure, the term "alkylenyl" as used herein by itself or part of another group refers to a divalent form of an alkyl group as defined above. In one embodiment, the alkylenyl is a divalent form of a C₁₋₆ alkyl. In one embodiment, the alkylenyl is a divalent form of a C₁₋₄ alkyl. Non-limiting exemplary alkylenyl groups include -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH(CH₃)CH₂-, and -CH₂C(CH₃)₂CH₂-.

[0111] For the purpose of the present disclosure, the term "cycloalkyl" as used by itself or as part of another group refers to saturated and partially unsaturated (containing one or two double bonds) cyclic aliphatic hydrocarbons containing one to three rings having from three to twelve carbon atoms (*i.e.*, C₃₋₁₂ cycloalkyl) or the number of carbons designated. In one embodiment, the cycloalkyl group has two rings. In one embodiment, the cycloalkyl group has one ring. In another embodiment, the cycloalkyl group is chosen from a C₃₋₈ cycloalkyl group. In another embodiment, the cycloalkyl group is chosen from a C₃₋₆ cycloalkyl group. Non-limiting exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, decalin, adamantyl, cyclohexenyl, spiro[3.3]heptane, and bicyclo[3.3.1]nonane.

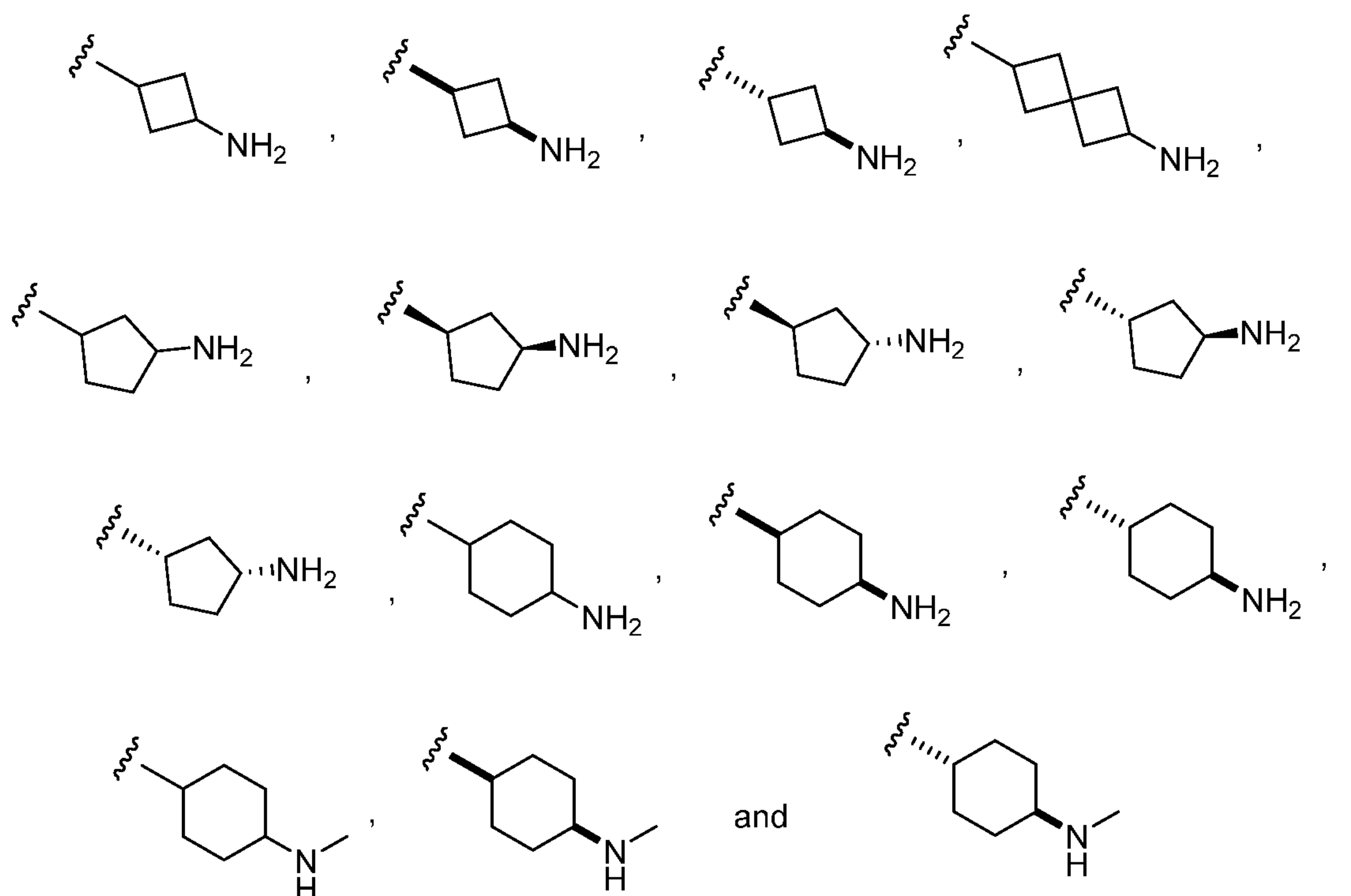
[0112] For the purpose of the present disclosure, the term "optionally substituted cycloalkyl" as used by itself or as part of another group means that the cycloalkyl as defined above is either unsubstituted or substituted with one, two, or three substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, cycloalkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyl, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, or (heteroaryl)alkyl. In one

embodiment, the optionally substituted cycloalkyl is substituted with two substituents. In another embodiment, the optionally substituted cycloalkyl is substituted with one substituent. In one embodiment, the optionally substituted cycloalkyl is an (amino)cycloalkyl. For the purpose of the present disclosure, the term "(amino)cycloalkyl" as used by itself or as part of another group means that the optionally substituted cycloalkyl as defined above is substituted with one amino or alkylamino group, and optionally one or two additional substituents. In one embodiment, the optionally substituted cycloalkyl is an (amino)cyclohexyl. For the purpose of the present disclosure, the term "(amino)cyclohexyl" as used by itself or as part of another group means that the optionally substituted cycloalkyl as defined above is a cyclohexyl group substituted with one amino or alkylamino group, and optionally one or two additional substituents. Non-limiting exemplary optionally substituted cycloalkyl groups include:

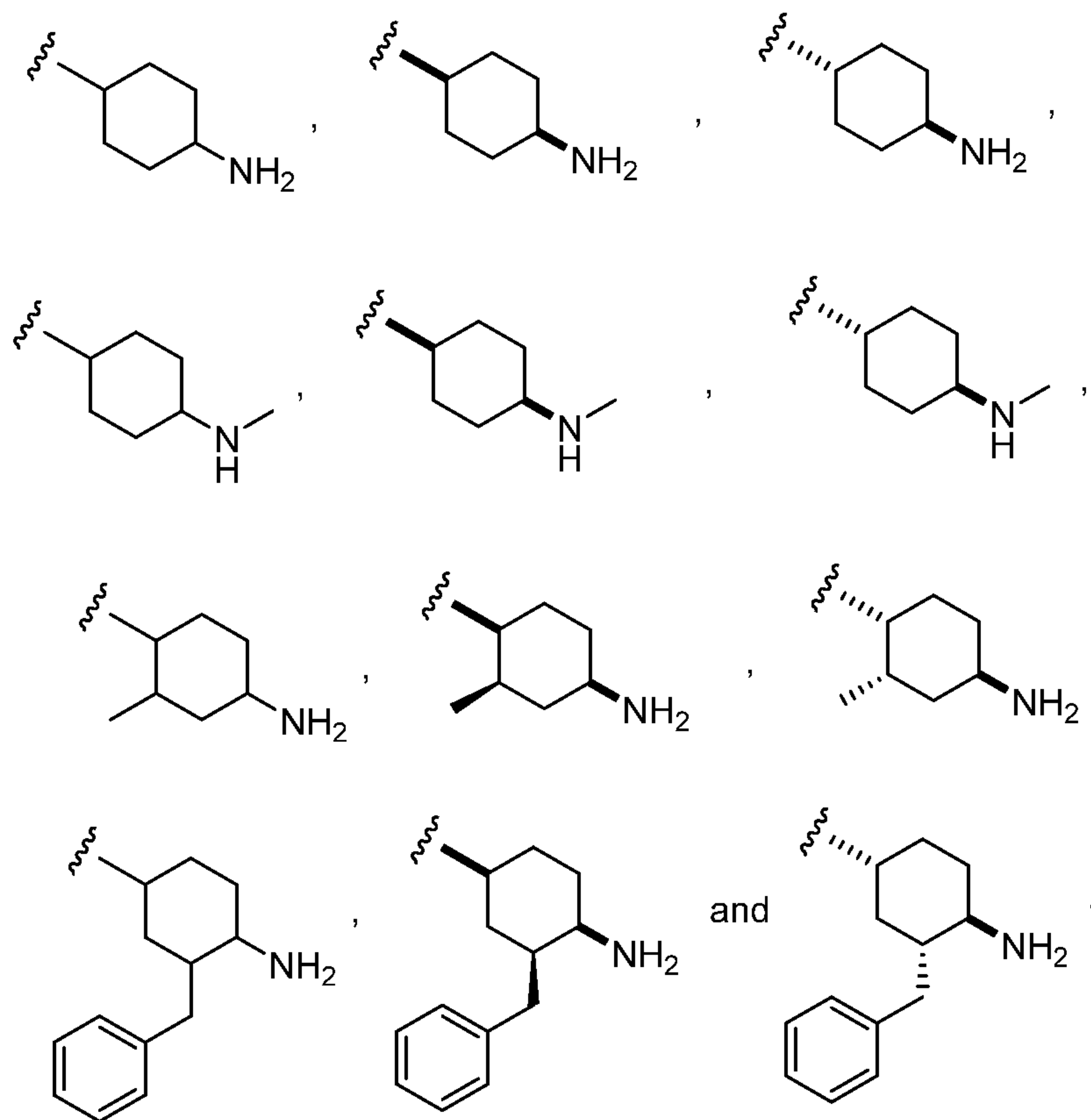




[0113] Non-limiting exemplary (amino)cycloalkyl groups include:

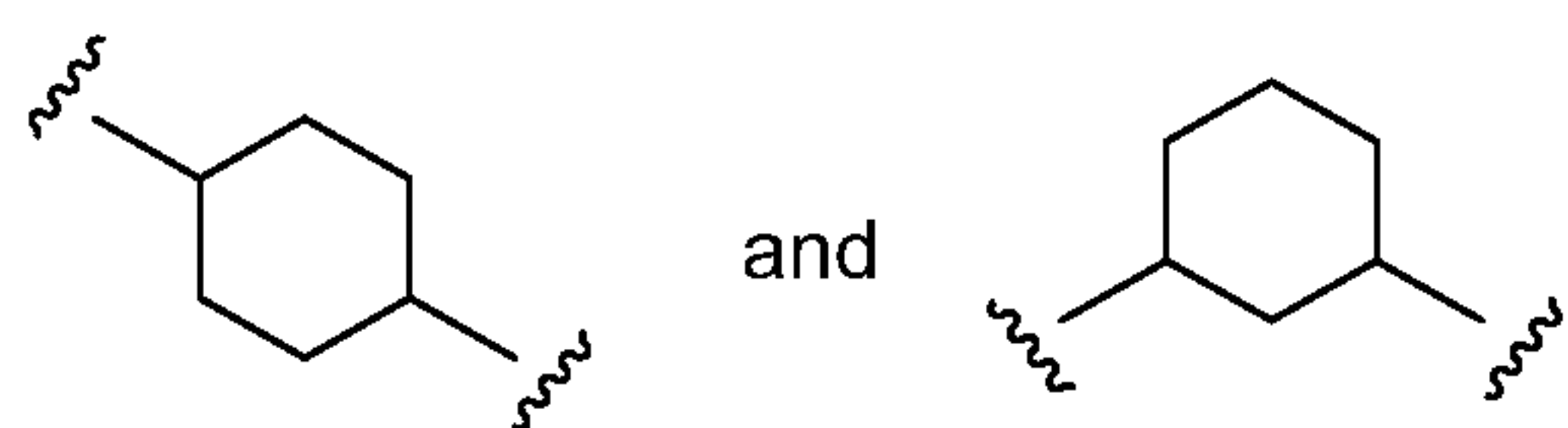


[0114] Non-limiting exemplary (amino)cyclohexyl groups include:

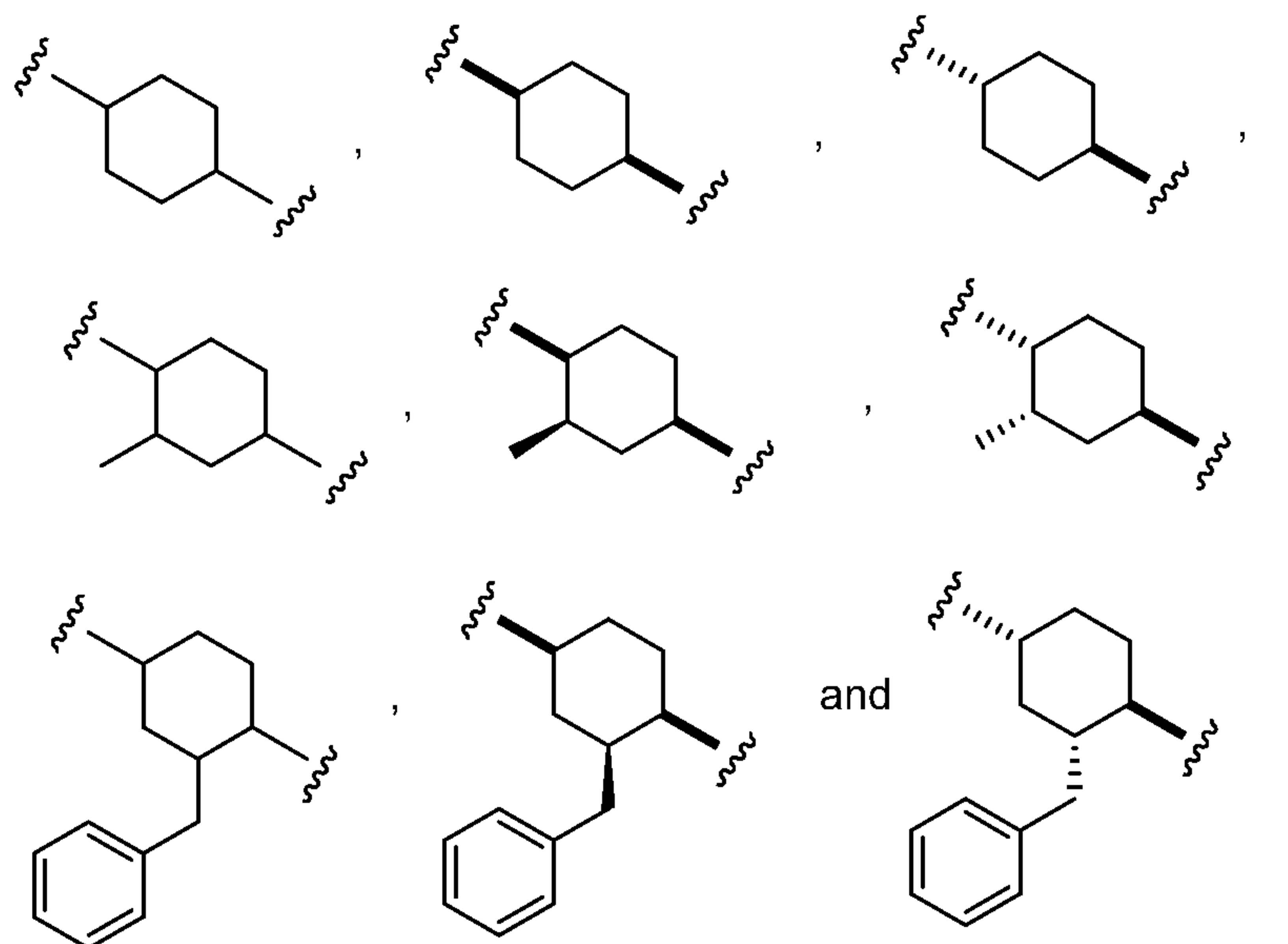


[0115] For the purpose of the present disclosure, the term "optionally substituted cyclohexyl" as used by itself or as part of another group means that the optionally substituted cycloalkyl as defined above is an optionally substituted cyclohexyl group.

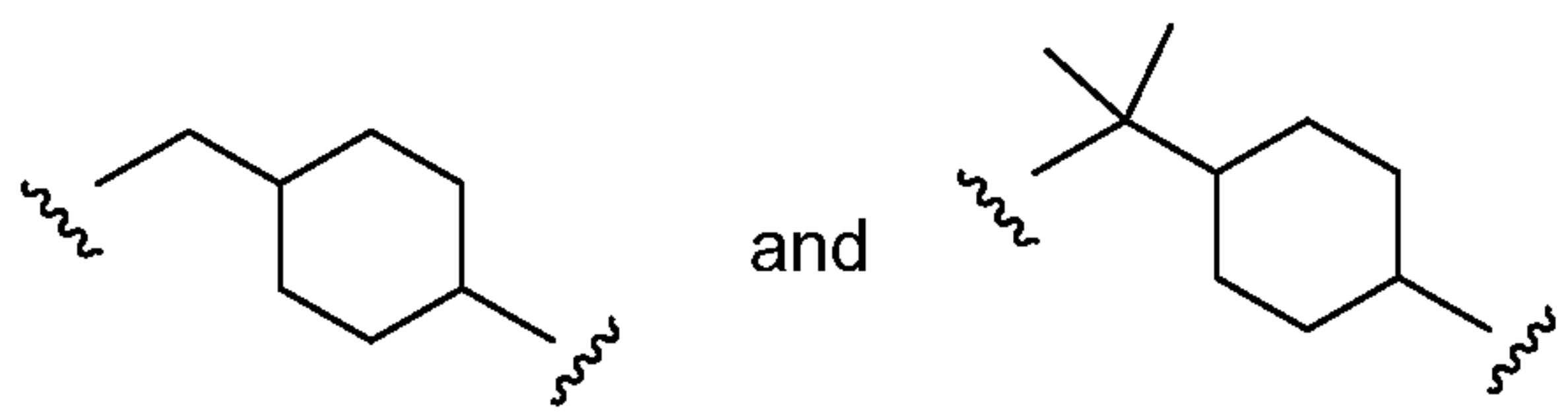
[0116] For the purpose of the present disclosure, the term "cycloalkylenyl" as used herein by itself or part of another group refers to a divalent form of an optionally substituted cycloalkyl group as defined above. In one embodiment, the cycloalkylenyl is a "cyclohexylenyl." The term "cyclohexylenyl" as used herein by itself or part of another group refers to a divalent form of an optionally substituted cyclohexyl group. Non-limiting exemplary cycloalkylenyl groups include:



[0117] For the purpose of the present disclosure, the term "1,4-cyclohexylenyl" as used herein by itself or part of another group refers to a cyclohexylenyl as defined above wherein the 1- and 4-positions of the cyclohexyl ring are substituted. Non-limiting exemplary 1,4-cyclohexylenyl groups include:



[0118] For the purpose of the present disclosure, the term "(cycloalkylenyl)alkyl" as used herein by itself or part of another group refers to an alkyl group substituted with a divalent form of an optionally substituted cycloalkyl group. In one embodiment, the cycloalkylenyl is a divalent form of optionally substituted cyclohexyl. In one embodiment, the alkyl is C_{1-4} alkyl. Non-limiting exemplary (cycloalkylenyl)alkyl groups include:



[0119] For the purpose of the present disclosure, the term "cycloalkenyl" as used by itself or part of another group refers to a partially unsaturated cycloalkyl group as defined above. In one embodiment, the cycloalkenyl has one carbon-to-carbon double bond. In another embodiment, the cycloalkenyl group is chosen from a C_{4-8} cycloalkenyl group. Exemplary cycloalkenyl groups include cyclopentenyl and cyclohexenyl.

[0120] For the purpose of the present disclosure, the term "optionally substituted cycloalkenyl" as used by itself or as part of another group means that the cycloalkenyl as defined above is either unsubstituted or substituted with one, two, or three substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, monohydroxyalkyl, dihydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl,

hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl. In one embodiment, the optionally substituted cycloalkenyl is substituted with two substituents. In another embodiment, the optionally substituted cycloalkenyl is substituted with one substituent. In another embodiment, the cycloalkenyl is unsubstituted.

[0121] For the purpose of the present disclosure, the term "alkenyl" as used by itself or as part of another group refers to an alkyl group as defined above containing one, two or three carbon-to-carbon double bonds. In one embodiment, the alkenyl group is chosen from a C₂₋₆ alkenyl group. In another embodiment, the alkenyl group is chosen from a C₂₋₄ alkenyl group. Non-limiting exemplary alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, *sec*-butenyl, pentenyl, and hexenyl.

[0122] For the purpose of the present disclosure, the term "optionally substituted alkenyl" as used herein by itself or as part of another group means the alkenyl as defined above is either unsubstituted or substituted with one, two or three substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclo.

[0123] For the purpose of the present disclosure, the term "alkynyl" as used by itself or as part of another group refers to an alkyl group as defined above containing one to three carbon-to-carbon triple bonds. In one embodiment, the alkynyl has one carbon-to-carbon triple bond. In one embodiment, the alkynyl group is chosen from a C₂₋₆ alkynyl group. In another embodiment, the alkynyl group is chosen from a C₂₋₄ alkynyl group. Non-limiting exemplary alkynyl groups include ethynyl, propynyl, butynyl, 2-butynyl, pentynyl, and hexynyl groups.

[0124] For the purpose of the present disclosure, the term "optionally substituted alkynyl" as used herein by itself or as part of another group means the alkynyl as defined above is either unsubstituted or substituted with one, two or three substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl,

arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclo.

[0125] For the purpose of the present disclosure, the term "haloalkyl" as used by itself or as part of another group refers to an alkyl group substituted by one or more fluorine, chlorine, bromine and/or iodine atoms. In one embodiment, the alkyl group is substituted by one, two, or three fluorine and/or chlorine atoms. In another embodiment, the haloalkyl group is chosen from a C₁₋₄ haloalkyl group. Non-limiting exemplary haloalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, and trichloromethyl groups.

[0126] For the purpose of the present disclosure, the term "fluoroalkyl" as used by itself or as part of another group refers to an alkyl group substituted by one or more fluorine atoms. In one embodiment, the alkyl group is substituted by one, two, or three fluorine atoms. In another embodiment, the fluoroalkyl group is chosen from a C₁₋₄ fluoroalkyl group. Non-limiting exemplary fluoroalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, and 4,4,4-trifluorobutyl.

[0127] For the purpose of the present disclosure, the term "hydroxyalkyl" as used by itself or as part of another group refers to an alkyl group substituted with one or more, *e.g.*, one, two, or three, hydroxy groups. In one embodiment, the hydroxyalkyl group is a monohydroxyalkyl group, *i.e.*, substituted with one hydroxy group. In another embodiment, the hydroxyalkyl group is a dihydroxyalkyl group, *i.e.*, substituted with two hydroxy groups. In another embodiment, the hydroxyalkyl group is chosen from a C₁₋₄ hydroxyalkyl group. Non-limiting exemplary hydroxyalkyl groups include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups, such as 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 3-hydroxybutyl, 4-hydroxybutyl, 2-hydroxy-1-methylpropyl, and 1,3-dihydroxyprop-2-yl.

[0128] For the purpose of the present disclosure, the term "alkoxy" as used by itself or as part of another group refers to an optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl or optionally substituted alkynyl attached to a terminal oxygen atom. In one embodiment, the alkoxy group is chosen from a C₁₋₄ alkoxy group. In another embodiment, the alkoxy group is chosen from a C₁₋₄ alkyl

attached to a terminal oxygen atom, *e.g.*, methoxy, ethoxy, *tert*-butoxy, $-\text{OCH}_2\text{C}\equiv\text{CH}$, $-\text{OCH}_2\text{C}\equiv\text{CCH}_3$, and $-\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$.

[0129] For the purpose of the present disclosure, the term "alkylthio" as used by itself or as part of another group refers to a sulfur atom substituted by an optionally substituted alkyl group. In one embodiment, the alkylthio group is chosen from a C_{1-4} alkylthio group. Non-limiting exemplary alkylthio groups include $-\text{SCH}_3$, and $-\text{SCH}_2\text{CH}_3$.

[0130] For the purpose of the present disclosure, the term "alkoxyalkyl" as used by itself or as part of another group refers to an alkyl group substituted with an alkoxy group. Non-limiting exemplary alkoxyalkyl groups include methoxymethyl, methoxyethyl, methoxypropyl, methoxybutyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, ethoxybutyl, propoxymethyl, iso-propoxymethyl, propoxyethyl, propoxypropyl, butoxymethyl, *tert*-butoxymethyl, isobutoxymethyl, *sec*-butoxymethyl, pentyloxymethyl, $-\text{CH}_2\text{OCH}_2\text{C}\equiv\text{CH}$ and $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$.

[0131] For the purpose of the present disclosure, the term "haloalkoxy" as used by itself or as part of another group refers to a haloalkyl attached to a terminal oxygen atom. Non-limiting exemplary haloalkoxy groups include fluoromethoxy, difluoromethoxy, trifluoromethoxy, and 2,2,2-trifluoroethoxy.

[0132] For the purpose of the present disclosure, the term "heteroalkyl" as used by itself or part of another group refers to a stable straight or branched chain hydrocarbon radical containing 1 to 10 carbon atoms and at least two heteroatoms, which can be the same or different, selected from O, N, or S, wherein: 1) the nitrogen atom(s) and sulfur atom(s) can optionally be oxidized; and/or 2) the nitrogen atom(s) can optionally be quaternized. The heteroatoms can be placed at any interior position of the heteroalkyl group or at a position at which the heteroalkyl group is attached to the remainder of the molecule. In one embodiment, the heteroalkyl group contains two oxygen atoms. In one embodiment, the heteroalkyl contains one oxygen and one nitrogen atom, *e.g.*, a (hydroxyalkylamino)alkyl group, *e.g.*, $-\text{CH}_2\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$. In one embodiment, the heteroalkyl contains two nitrogen atoms. Non-limiting exemplary heteroalkyl groups include $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{NHCH}_2\text{CH}_2\text{OCH}_2$, $-\text{OCH}_2\text{CH}_2\text{NH}_2$, $-\text{NHCH}_2\text{CH}_2\text{N}(\text{H})\text{CH}_3$, $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{N}(\text{H})\text{CH}_2\text{CH}_3$, and $-\text{OCH}_2\text{CH}_2\text{OCH}_3$.

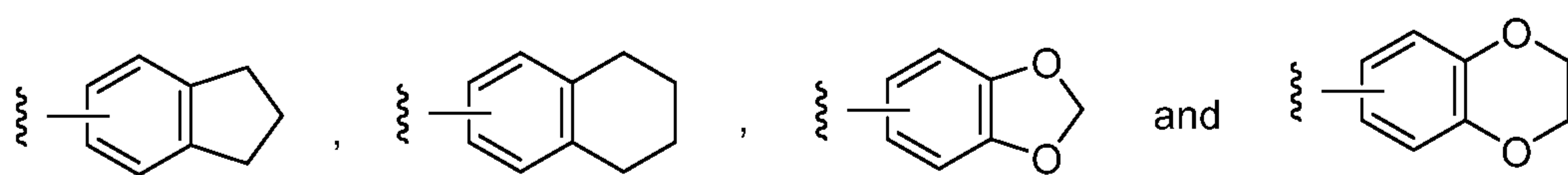
[0133] For the purpose of the present disclosure, the term "aryl" as used by itself or as part of another group refers to a monocyclic or bicyclic aromatic ring system having from

six to fourteen carbon atoms (*i.e.*, C₆₋₁₄ aryl). Non-limiting exemplary aryl groups include phenyl (abbreviated as "Ph"), naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl, and fluorenyl groups. In one embodiment, the aryl group is chosen from phenyl or naphthyl. In one embodiment, the aryl group is phenyl.

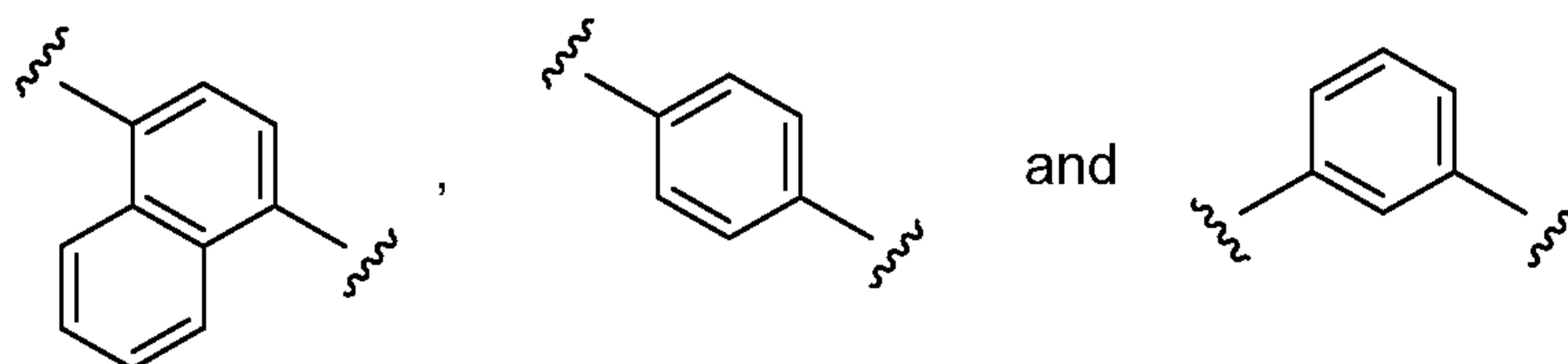
[0134] For the purpose of the present disclosure, the term "optionally substituted aryl" as used herein by itself or as part of another group means that the aryl as defined above is either unsubstituted or substituted with one to five substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, aralkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, heteroaryloxy, aralkyl, aralkyloxy, (aralkyloxy)alkyl, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, heteroalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, (C₁₋₄ haloalkoxy)alkyl, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, (carboxamido)alkyl-O-, mercaptoalkyl, (heterocyclo)alkyl, (heterocyclo)alkyl-O-, (cycloalkylamino)alkyl, (hydroxyalkylamino)alkyl, (amino)(heteroaryl)alkyl, (heterocycloamino)alkyl, (amino)(hydroxy)alkyl, (heteroaryl)alkyl, (heteroaryl)alkyl-O-, -N(R⁴³)(R⁴⁴), -CH₂N(R⁴³)(R⁴⁴), -CH₂N(H)C(=O)-R⁴⁵, and -N(H)C(=O)-R⁴⁵, wherein R⁴³ is hydrogen, C₁₋₄ alkyl, optionally substituted aryl, or optionally substituted heteroaryl; R⁴⁴ is alkoxyalkyl, (heterocyclo)alkyl, (amino)alkyl, (alkylamino)alkyl, aralkyl, or (dialkylamino)alkyl; and R⁴⁵ is alkyl, alkoxyalkyl, (heterocyclo)alkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, optionally substituted aryl, optionally substituted heteroaryl, aralkyl, or (heteroaryl)alkyl. In another embodiment, the optionally substituted aryl is substituted with one to five substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, heteroaryloxy, aralkyl, aralkyloxy, (aralkyloxy)alkyl, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, heteroalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, (C₁₋₄ haloalkoxy)alkyl, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl,

(cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, (cycloalkylamino)alkyl, (hydroxyalkylamino)alkyl, (amino)(heteroaryl)alkyl, (heterocycloamino)alkyl, (amino)(hydroxy)alkyl, (heteroaryl)alkyl, $-N(R^{43})(R^{44})$, $-CH_2N(H)C(=O)-R^{45}$, and $-N(H)C(=O)-R^{45}$.

[0135] In one embodiment, the optionally substituted aryl is an optionally substituted phenyl. In one embodiment, the optionally substituted phenyl has four substituents. In another embodiment, the optionally substituted phenyl has three substituents. In another embodiment, the optionally substituted phenyl has two substituents. In another embodiment, the optionally substituted phenyl has one substituent. In another embodiment, the optionally substituted phenyl has at least one amino, alkylamino, dialkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (amino)(heteroaryl)alkyl, or (amino)(hydroxy)alkyl substituent. Non-limiting exemplary substituted aryl groups include 2-methylphenyl, 2-methoxyphenyl, 2-fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 3-methylphenyl, 3-methoxyphenyl, 3-fluorophenyl, 3-chlorophenyl, 4-methylphenyl, 4-ethylphenyl, 4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 2,6-di-fluorophenyl, 2,6-di-chlorophenyl, 2-methyl, 3-methoxyphenyl, 2-ethyl, 3-methoxyphenyl, 3,4-di-methoxyphenyl, 3,5-di-fluorophenyl, 3,5-di-methylphenyl, 3,5-dimethoxy, 4-methylphenyl, 2-fluoro-3-chlorophenyl, 3-chloro-4-fluorophenyl, and 2-phenylpropan-2-amine. The term optionally substituted aryl is meant to include aryl groups having fused optionally substituted cycloalkyl and fused optionally substituted heterocyclo rings. Examples include:.



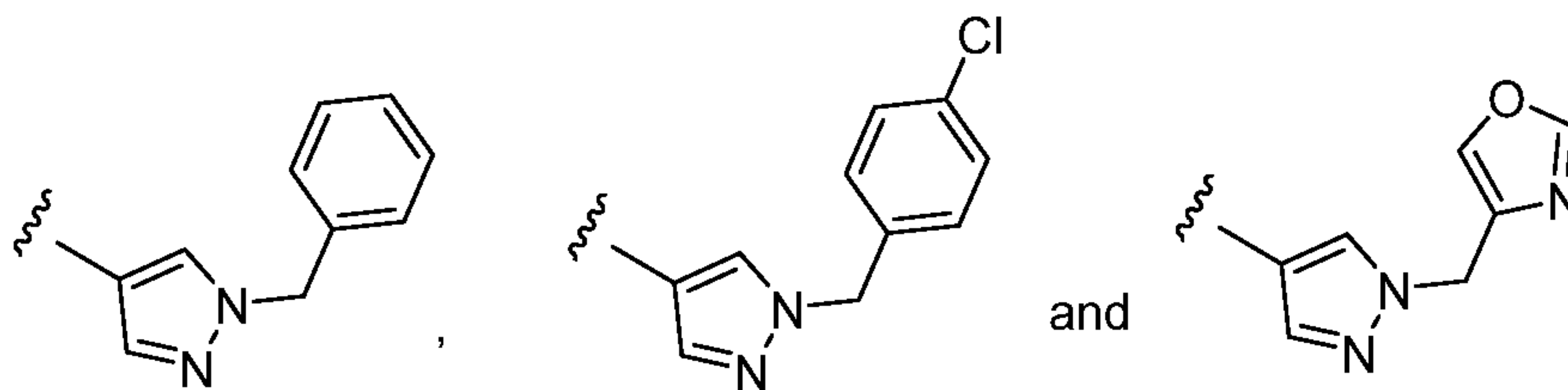
[0136] For the purpose of the present disclosure, the term "arylenyl" as used herein by itself or part of another group refers to a divalent form of an optionally substituted aryl group as defined above. In one embodiment, the arylenyl is a divalent form of an optionally substituted phenyl. In one embodiment, the arylenyl is a divalent form of phenyl. Non-limiting exemplary alkylenyl groups include:



- [0137] For the purpose of the present disclosure, the term "aryloxy" as used by itself or as part of another group refers to an optionally substituted aryl attached to a terminal oxygen atom. A non-limiting exemplary aryloxy group is PhO-.
- [0138] For the purpose of the present disclosure, the term "heteroaryloxy" as used by itself or as part of another group refers to an optionally substituted heteroaryl attached to a terminal oxygen atom.
- [0139] For the purpose of the present disclosure, the term "aralkyloxy" or "arylalkyloxy" as used by itself or as part of another group refers to an aralkyl group attached to a terminal oxygen atom. A non-limiting exemplary aralkyloxy group is PhCH₂O-.
- [0140] For the purpose of the present disclosure, the term "(aralkyloxy)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with an aralkyloxy group. In one embodiment, the alkyl is a C₁₋₄ alkyl. Non-limiting exemplary "(aralkyloxy)alkyl" groups include -CH₂OCH₂(3-F-Ph) and -CH₂OCH₂CH₂CH₂(2-OMe-Ph).
- [0141] For the purpose of the present disclosure, the term "heteroaryl" or "heteroaromatic" refers to monocyclic and bicyclic aromatic ring systems having 5 to 14 ring atoms (*i.e.*, a 5- to 14-membered heteroaryl) and 1, 2, 3, or 4 heteroatoms independently chosen from oxygen, nitrogen, or sulfur. In one embodiment, the heteroaryl has three heteroatoms. In another embodiment, the heteroaryl has two heteroatoms. In another embodiment, the heteroaryl has one heteroatom. In one embodiment, the heteroaryl has 5 ring atoms, *e.g.*, thienyl, a 5-membered heteroaryl having four carbon atoms and one sulfur atom. In another embodiment, the heteroaryl has 6 ring atoms, *e.g.*, pyridyl, a 6-membered heteroaryl having five carbon atoms and one nitrogen atom. Non-limiting exemplary heteroaryl groups include thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, benzofuryl, pyranlyl, isobenzofuranyl, benzooxazonyl, chromenyl, xanthenyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, cinnolinyl, quinazolinyl, pteridinyl, 4*aH*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, thiazolyl, isothiazolyl, phenothiazolyl, isoxazolyl, furazanyl, and phenoxazinyl. In one embodiment, the heteroaryl is chosen from thienyl (*e.g.*, thien-2-yl and thien-3-yl), furyl (*e.g.*, 2-furyl and 3-furyl), pyrrolyl (*e.g.*, 1*H*-pyrrol-2-yl and 1*H*-pyrrol-3-yl), imidazolyl

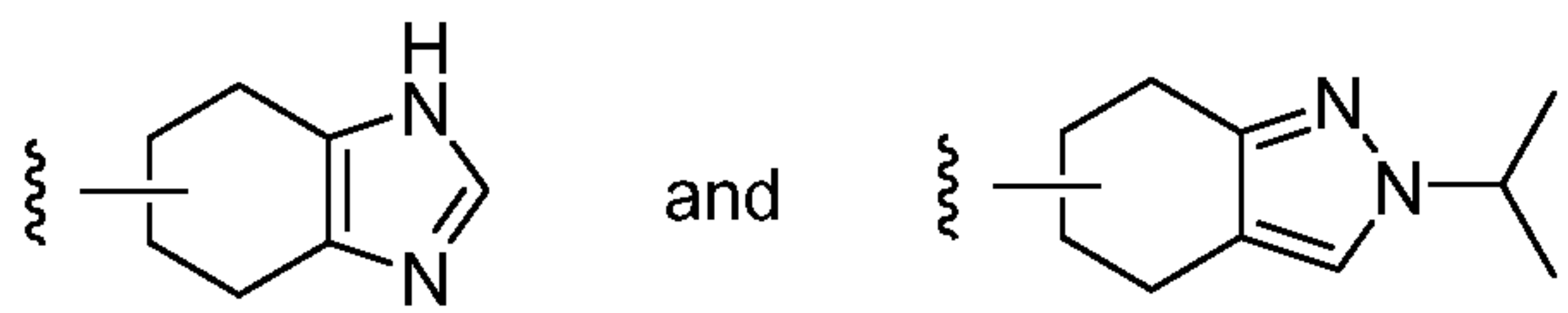
(*e.g.*, 2H-imidazol-2-yl and 2H-imidazol-4-yl), pyrazolyl (*e.g.*, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, and 1H-pyrazol-5-yl), pyridyl (*e.g.*, pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl), pyrimidinyl (*e.g.*, pyrimidin-2-yl, pyrimidin-4-yl, and pyrimidin-5-yl), thiazolyl (*e.g.*, thiazol-2-yl, thiazol-4-yl, and thiazol-5-yl), isothiazolyl (*e.g.*, isothiazol-3-yl, isothiazol-4-yl, and isothiazol-5-yl), oxazolyl (*e.g.*, oxazol-2-yl, oxazol-4-yl, and oxazol-5-yl) and isoxazolyl (*e.g.*, isoxazol-3-yl, isoxazol-4-yl, and isoxazol-5-yl). The term "heteroaryl" is also meant to include possible N-oxides. Exemplary N-oxides include pyridyl N-oxide.

[0142] For the purpose of the present disclosure, the term "optionally substituted heteroaryl" as used by itself or as part of another group means that the heteroaryl as defined above is either unsubstituted or substituted with one to four substituents, *e.g.*, one or two substituents, independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aralkyl, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, $-N(R^{43})(R^{44})$, or $-N(H)C(=O)-R^{45}$, wherein R^{43} is hydrogen or C_{1-4} alkyl; R^{44} is alkoxyalkyl, (heterocyclo)alkyl, (amino)alkyl, (alkylamino)alkyl, or (dialkylamino)alkyl; and R^{45} is alkyl, optionally substituted aryl, or optionally substituted heteroaryl. In one embodiment, the optionally substituted heteroaryl has one substituent. In one embodiment, the substituent is amino, alkylamino, dialkylamino, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkyl, $-N(R^{43})(R^{44})$, or $-N(H)C(=O)-R^{45}$. In another embodiment, the substituent is aralkyl or (heteroaryl)alkyl. Examples include:

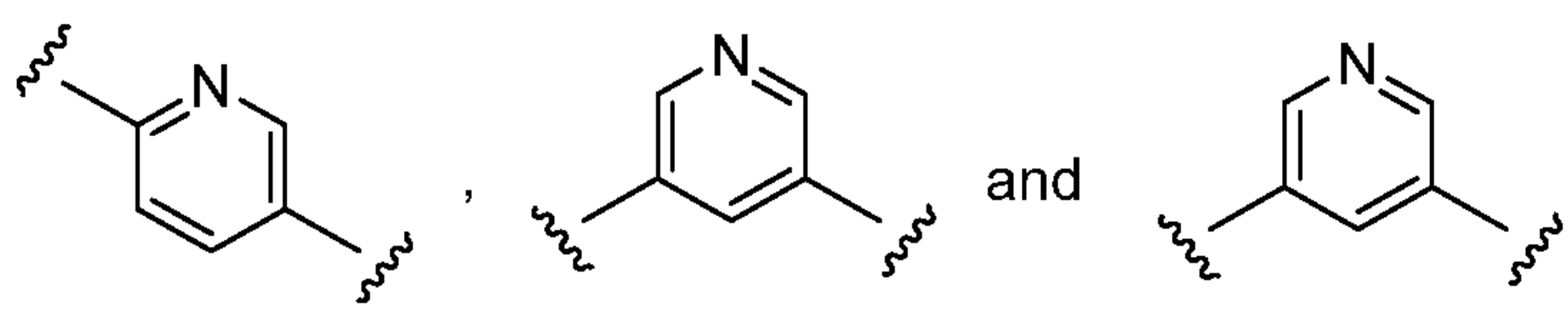


In one embodiment, the optionally substituted is an optionally substituted pyridyl, *i.e.*, 2-, 3-, or 4-pyridyl. Any available carbon or nitrogen atom can be substituted. The term

optionally substituted heteroaryl is meant to include heteroaryl groups having fused optionally substituted cycloalkyl and fused optionally substituted heterocyclo rings. Examples include:



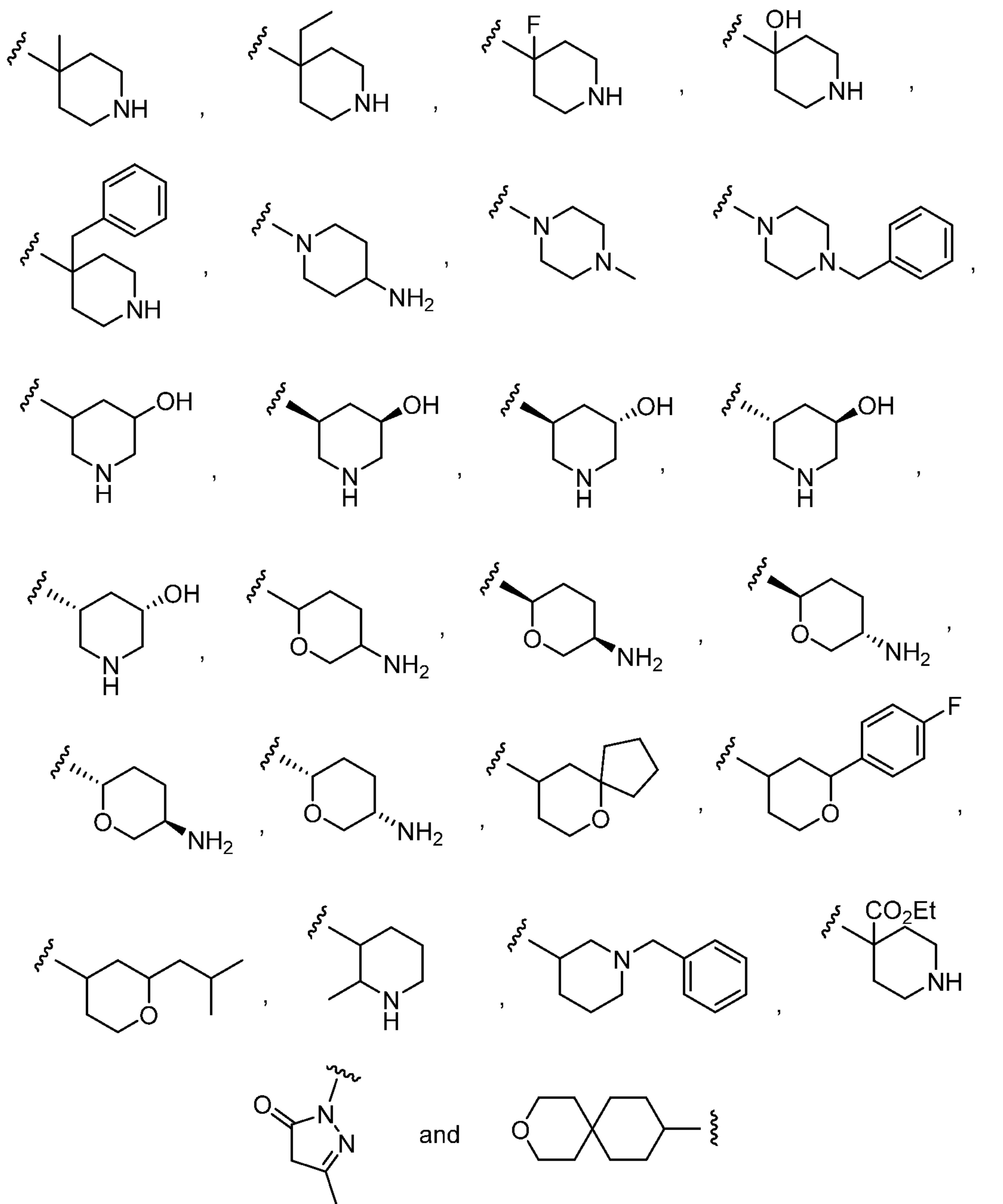
[0143] For the purpose of the present disclosure, the term "heteroarylenyl" as used herein by itself or part of another group refers to a divalent form of an optionally substituted heteroaryl group as defined above. In one embodiment, the heteroarylenyl is a divalent form of an optionally substituted pyridyl. Non-limiting exemplary heteroarylenyl groups include:



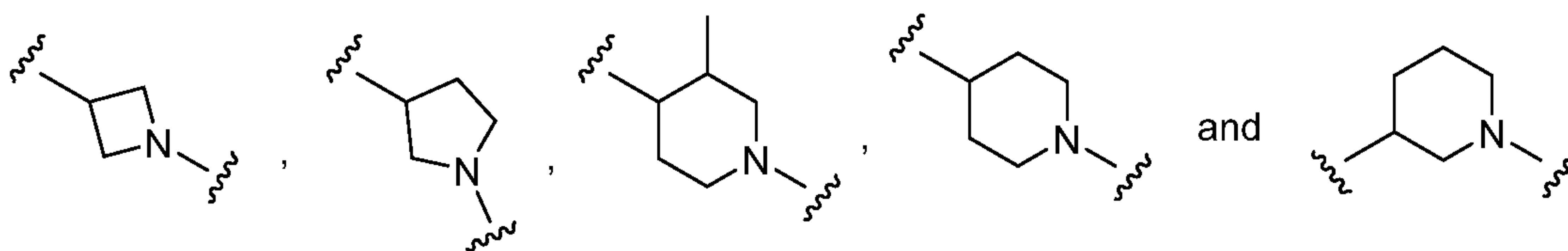
[0144] For the purpose of the present disclosure, the term "heterocycle" or "heterocyclo" as used by itself or as part of another group refers to saturated and partially unsaturated (*e.g.*, containing one or two double bonds) cyclic groups containing one, two, or three rings having from three to fourteen ring members (*i.e.*, a 3- to 14-membered heterocyclo) and at least one heteroatom. Each heteroatom is independently selected from the group consisting of oxygen, sulfur, including sulfoxide and sulfone, and/or nitrogen atoms, which can be quaternized. The term "heterocyclo" is meant to include cyclic ureido groups such as imidazolidinyl-2-one, cyclic amide groups such as β -lactam, γ -lactam, δ -lactam and ϵ -lactam, and cyclic carbamate groups such as oxazolidinyl-2-one. The term "heterocyclo" is also meant to include groups having fused optionally substituted aryl groups, *e.g.*, indolinyl, indolinyl-2-one, benzo[d]oxazolyl-2(3H)-one. In one embodiment, the heterocyclo group is chosen from a 4-, 5-, 6-, 7- or 8-membered cyclic group containing one ring and one or two oxygen and/or nitrogen atoms. In one embodiment, the heterocyclo group is chosen from a 5- or 6-membered cyclic group containing one ring and one or two nitrogen atoms. In one embodiment, the heterocyclo group is chosen from a 8-, 9-, 10-, 11-, or 12-membered cyclic group containing two rings and one or two nitrogen atoms. The heterocyclo can be optionally linked to the rest of the molecule through a carbon or nitrogen atom. Non-limiting exemplary heterocyclo groups include 2-oxopyrrolidin-3-yl, 2-imidazolidinone, piperidinyl, morpholinyl,

piperazinyl, pyrrolidinyl, 8-azabicyclo[3.2.1]octane (nortropine), 6-azaspiro[2.5]octane, 6-azaspiro[3.4]octane, indolinyl, indolinyl-2-one, 1,3-dihydro-2H-benzo[d]imidazol-2-one

[0145] For the purpose of the present disclosure, the term "optionally substituted heterocyclo" as used herein by itself or part of another group means the heterocyclo as defined above is either unsubstituted or substituted with one to four substituents independently selected from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, aralkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyl, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl. Substitution may occur on any available carbon or nitrogen atom, and may form a spirocycle. In another embodiment, the optionally substituted heterocyclo is substituted with one to four substituents independently selected from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyl, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl. In one embodiment, the optionally substituted heterocyclo is substituted with at least one amino, alkylamino, or dialkylamino group. Non-limiting exemplary optionally substituted heterocyclo groups include:

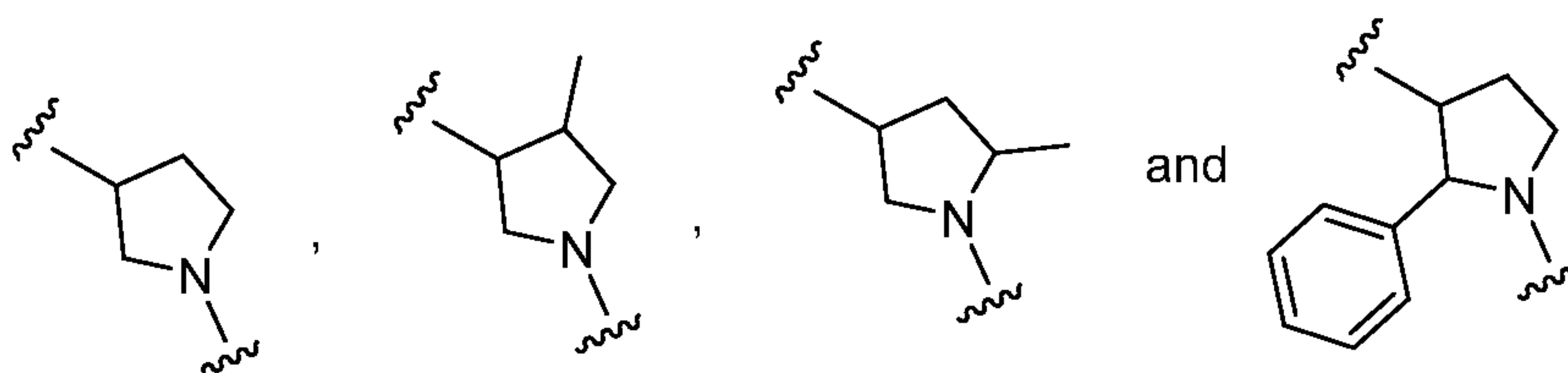


[0146] For the purpose of the present disclosure, the term "heterocyclenyl" as used herein by itself or part of another group refers to a divalent form of an optionally substituted heterocyclo group as defined above. In one embodiment, the heterocyclenyl is a divalent form of an optionally substituted azetidine. In one embodiment, the heterocyclenyl is a divalent form of an optionally substituted piperidinyl. Non-limiting exemplary heterocyclenyl groups include:



[0147] For the purpose of the present disclosure, the term "optionally substituted pyrrolidinyl" as used by itself or as part of another group means that the optionally substituted heterocycle as defined above is an optionally substituted pyrrolidinyl group.

[0148] For the purpose of the present disclosure, the term "optionally substituted pyrrolidinenyl" as used herein by itself or part of another group refers to a divalent form of an optionally substituted pyrrolidinyl group as defined above. Non-limiting exemplary optionally substituted pyrrolidinenyl groups include:



[0149] For the purpose of the present disclosure, the term "amino" as used by itself or as part of another group refers to -NH_2 .

[0150] For the purpose of the present disclosure, the term "alkylamino" as used by itself or as part of another group refers to -NHR^{22} , wherein R^{22} is C_{1-6} alkyl. In one embodiment, R^{22} is C_{1-4} alkyl. Non-limiting exemplary alkylamino groups include -N(H)CH_3 and $\text{-N(H)CH}_2\text{CH}_3$.

[0151] For the purpose of the present disclosure, the term "dialkylamino" as used by itself or as part of another group refers to $\text{-NR}^{23a}\text{R}^{23b}$, wherein R^{23a} and R^{23b} are each independently C_{1-6} alkyl. In one embodiment, R^{23a} and R^{23b} are each independently C_{1-4} alkyl. Non-limiting exemplary dialkylamino groups include $\text{-N(CH}_3)_2$ and $\text{-N(CH}_3)\text{CH}_2\text{CH(CH}_3)_2$.

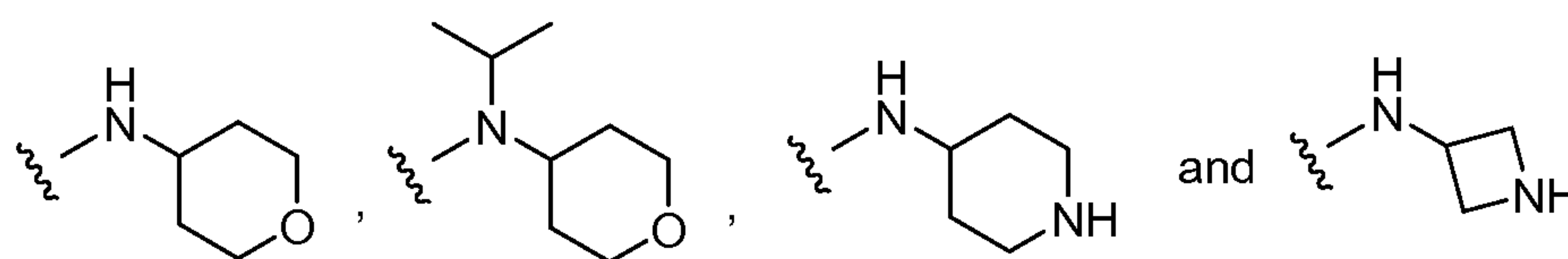
[0152] For the purpose of the present disclosure, the term "hydroxyalkylamino" as used by itself or as part of another group refers to $\text{-NR}^{24a}\text{R}^{24b}$, wherein R^{24a} is hydrogen or C_{1-4} alkyl, and R^{24b} is hydroxyalkyl. Non-limiting exemplary hydroxyalkylamino groups include $\text{-N(H)CH}_2\text{CH}_2\text{OH}$, $\text{-N(H)CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{-N(CH}_3)\text{CH}_2\text{CH}_2\text{OH}$, and $\text{-N(CH}_3)\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$.

[0153] For the purpose of the present disclosure, the term "(hydroxyalkylamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with an

hydroxyalkylamino group. In one embodiment, the alkyl is a C₁₋₄ alkyl. A non-limiting exemplary (hydroxyalkylamino)alkyl group is -CH₂N(CH₃)CH₂CH₂CH₂OH.

[0154] For the purpose of the present disclosure, the term "cycloalkylamino" as used by itself or as part of another group refers to -NR^{25a}R^{25b}, wherein R^{25a} is optionally substituted cycloalkyl and R^{25b} is hydrogen or C₁₋₄ alkyl.

[0155] For the purpose of the present disclosure, the term "heterocycloamino" as used by itself or as part of another group refers to -NR^{25c}R^{25d}, wherein R^{25c} is optionally substituted heterocyclo and R^{25d} is hydrogen or C₁₋₄ alkyl. Non-limiting exemplary heterocycloamino groups include:



[0156] For the purpose of the present disclosure, the term "(heterocycloamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with an heterocycloamino group. In one embodiment, the alkyl is a C₁₋₄ alkyl.

[0157] For the purpose of the present disclosure, the term "aralkylamino" as used by itself or as part of another group refers to -NR^{26a}R^{26b}, wherein R^{26a} is aralkyl and R^{26b} is hydrogen or C₁₋₄ alkyl. Non-limiting exemplary aralkylamino groups include -N(H)CH₂Ph and -N(CH₃)CH₂Ph.

[0158] For the purpose of the present disclosure, the term "(amino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with an amino group. In one embodiment, the alkyl is a C₁₋₄ alkyl. Non-limiting exemplary (amino)alkyl groups include -CH₂NH₂, -C(NH₂)(H)CH₃, -CH₂CH₂NH₂, -CH₂C(NH₂)(H)CH₃, -CH₂CH₂CH₂NH₂, -CH₂CH₂CH₂CH₂NH₂, and -CH₂C(CH₃)₂CH₂NH₂.

[0159] For the purpose of the present disclosure, the term "(alkylamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with an alkylamino group. In one embodiment, the alkyl is a C₁₋₄ alkyl. A non-limiting exemplary (alkylamino)alkyl group is -CH₂CH₂N(H)CH₃.

[0160] For the purpose of the present disclosure, the term "(dialkylamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted by a dialkylamino group. In one embodiment, the alkyl is a C₁₋₄ alkyl. Non-limiting exemplary (dialkylamino)alkyl groups are -CH₂CH₂N(CH₃)₂.

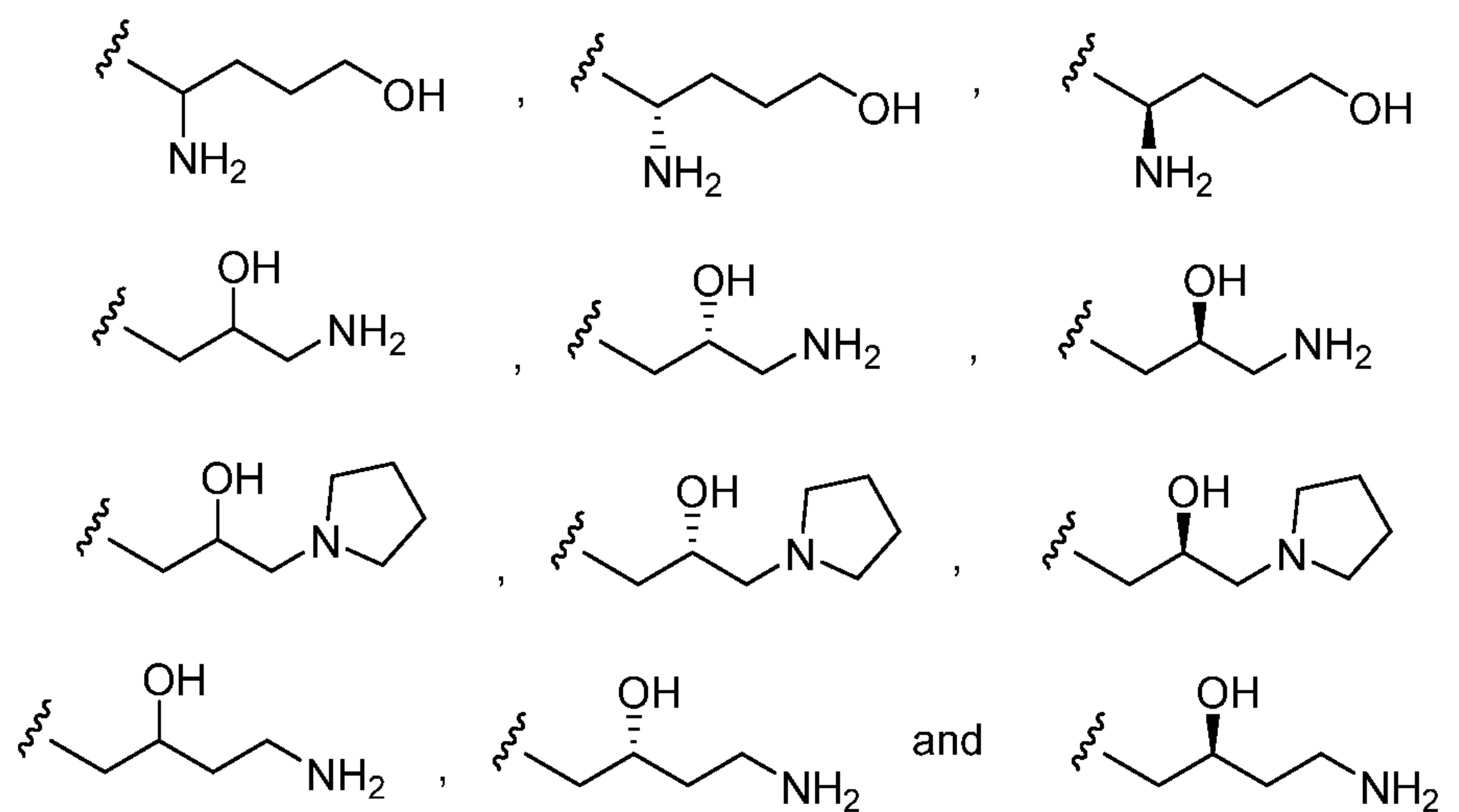
[0161] For the purpose of the present disclosure, the term "(cycloalkylamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted by a cycloalkylamino group. In one embodiment, the alkyl is a C₁₋₄ alkyl. Non-limiting exemplary (cycloalkylamino)alkyl groups include -CH₂N(H)cyclopropyl, -CH₂N(H)cyclobutyl, and -CH₂N(H)cyclohexyl.

[0162] For the purpose of the present disclosure, the term "(aralkylamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with an aralkylamino group. In one embodiment, the alkyl is a C₁₋₄ alkyl. A non-limiting exemplary (aralkylamino)alkyl group is -CH₂CH₂CH₂N(H)CH₂Ph.

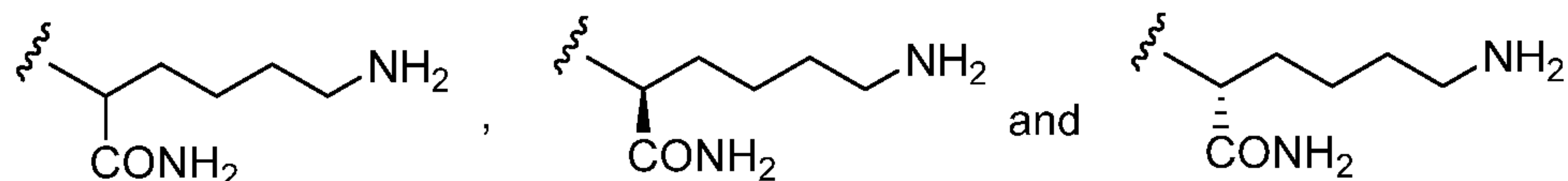
[0163] For the purpose of the present disclosure, the term "(hydroxyalkylamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with an hydroxyalkylamino group. A non-limiting exemplary (hydroxyalkylamino)alkyl group is -CH₂CH₂NHCH₂CH₂OH

[0164] For the purpose of the present disclosure, the term "(cyano)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one or more cyano, *e.g.*, -CN, groups. In one embodiment, the alkyl is a C₁₋₄ alkyl. Non-limiting exemplary (cyano)alkyl groups include -CH₂CH₂CN, -CH₂CH₂CH₂CN, and -CH₂CH₂CH₂CH₂CN.

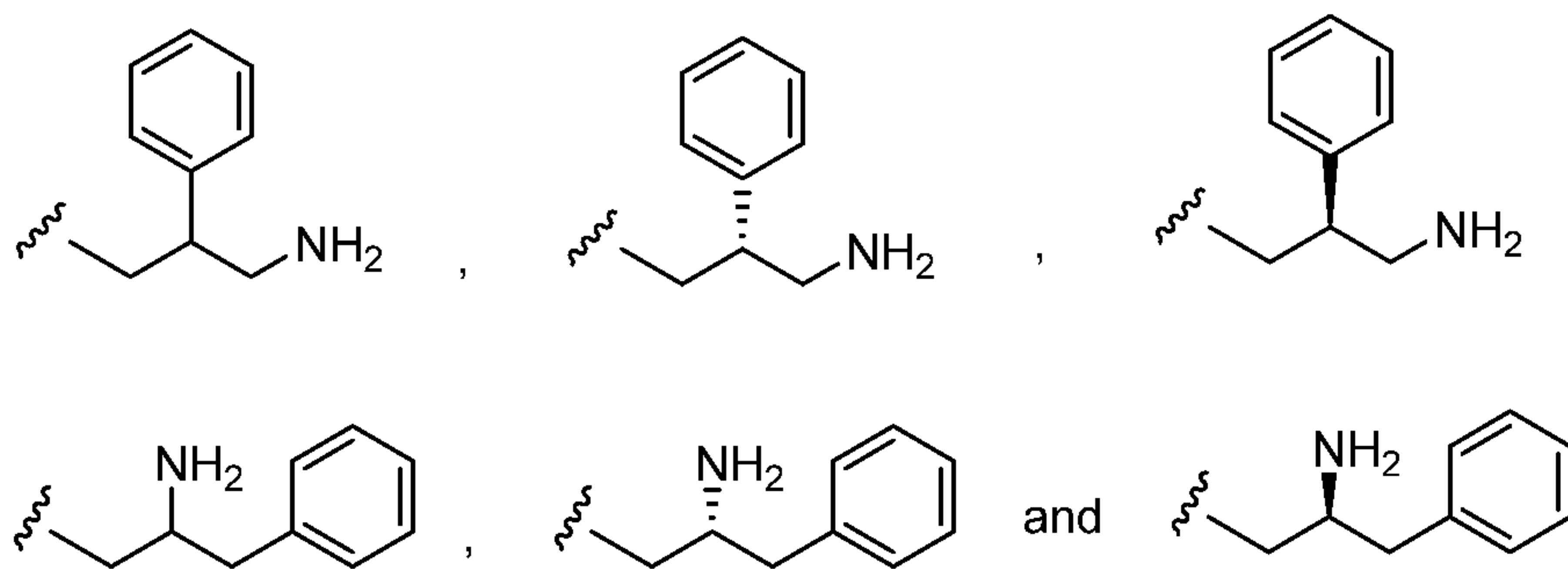
[0165] For the purpose of the present disclosure, the term "(amino)(hydroxy)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one amino, alkylamino, dialkylamino, or heterocyclo group and one hydroxy group. In one embodiment, the alkyl is a C₁₋₆ alkyl. In another embodiment, the alkyl is a C₁₋₄ alkyl. Non-limiting exemplary (amino)(hydroxy)alkyl groups include:



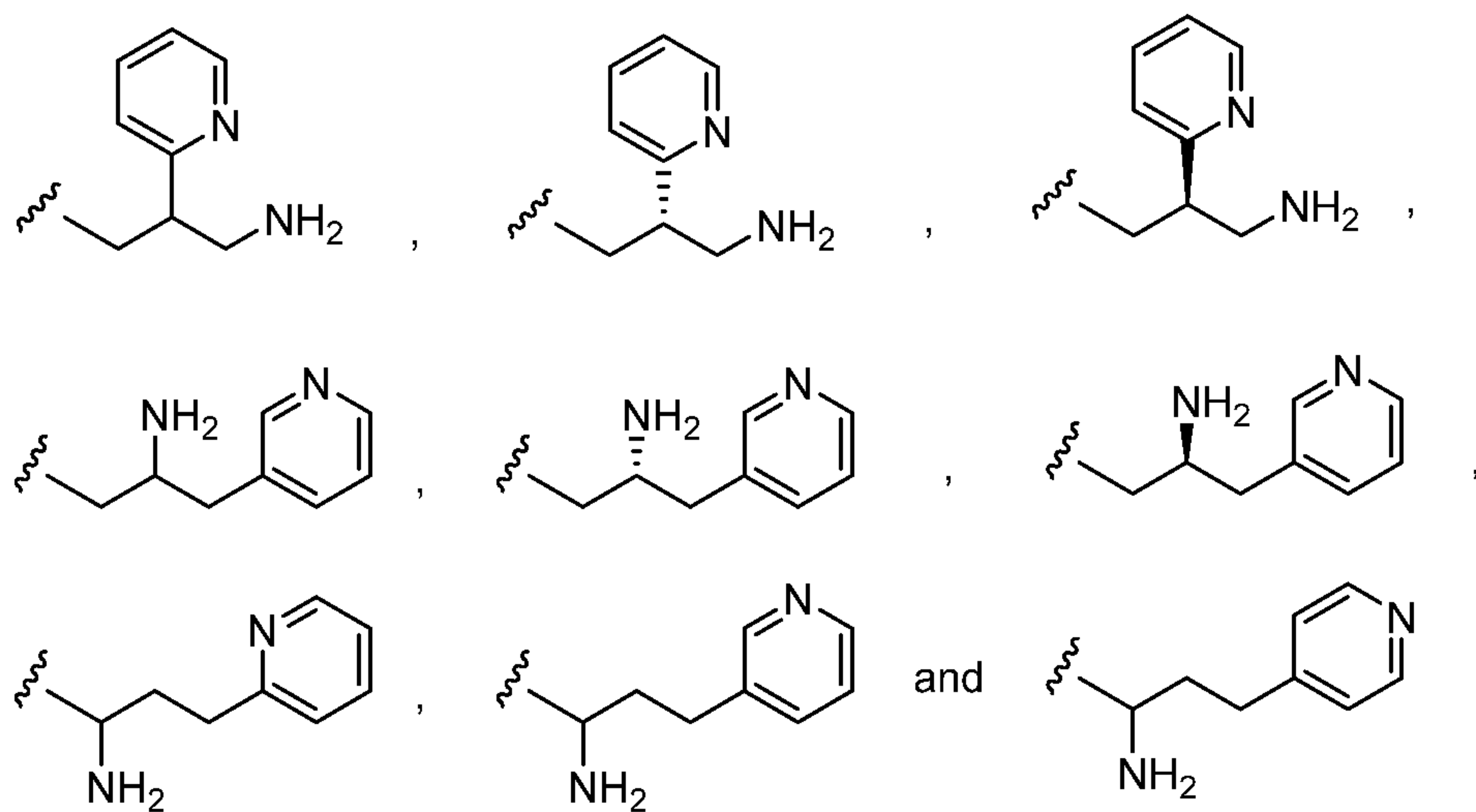
[0166] For the purpose of the present disclosure, the term "(amino)(carboxamido)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one amino, alkylamino, or dialkylamino, and one carboxamido group. In one embodiment, the alkyl is a C₁₋₆ alkyl. Non-limiting exemplary (amino)(carboxamido)alkyl groups include:



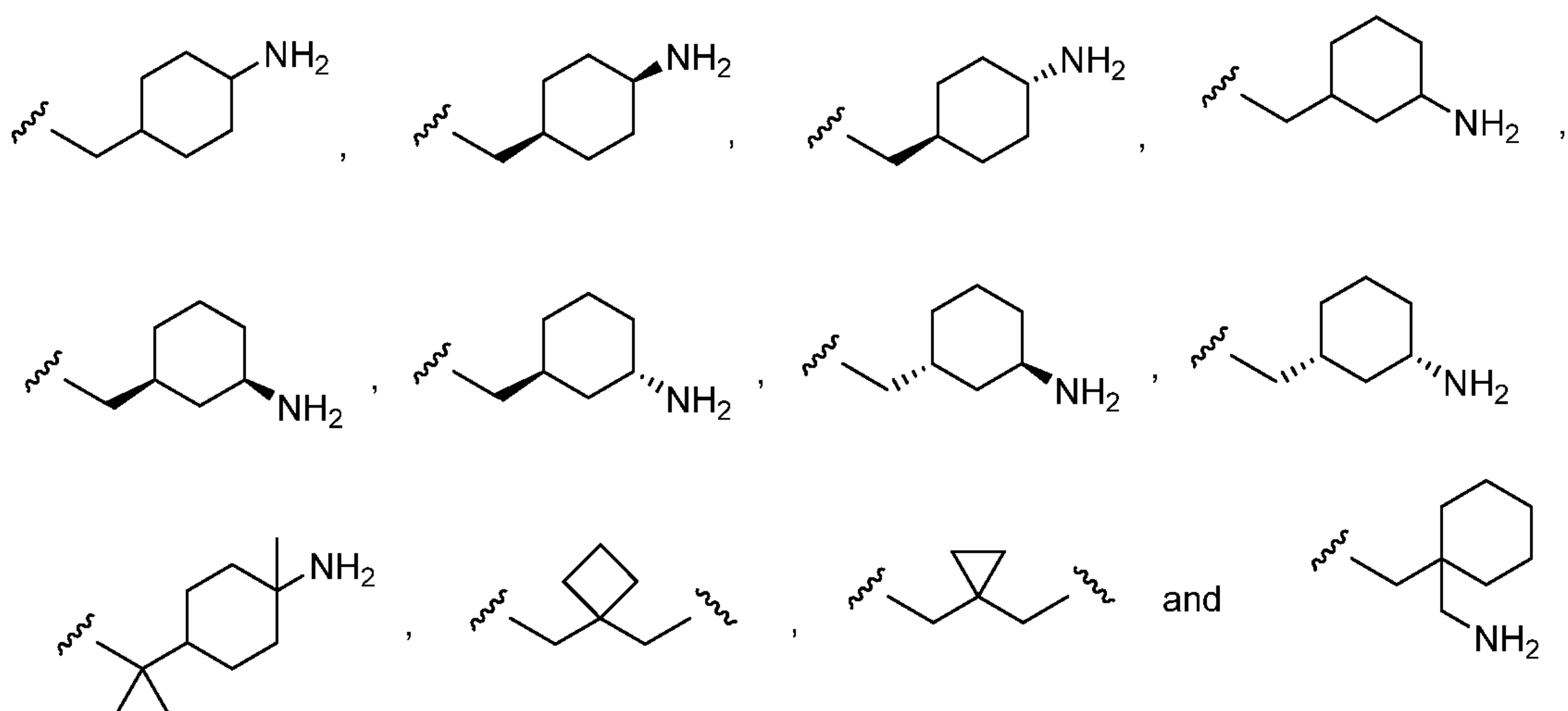
[0167] For the purpose of the present disclosure, the term "(amino)(aryl)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one amino, alkylamino, or dialkylamino group and one optionally substituted aryl group. In one embodiment, the alkyl is a C₁₋₆ alkyl. In one embodiment, the optionally substituted aryl group is an optionally substituted phenyl. Non-limiting exemplary (amino)(aryl)alkyl groups include:



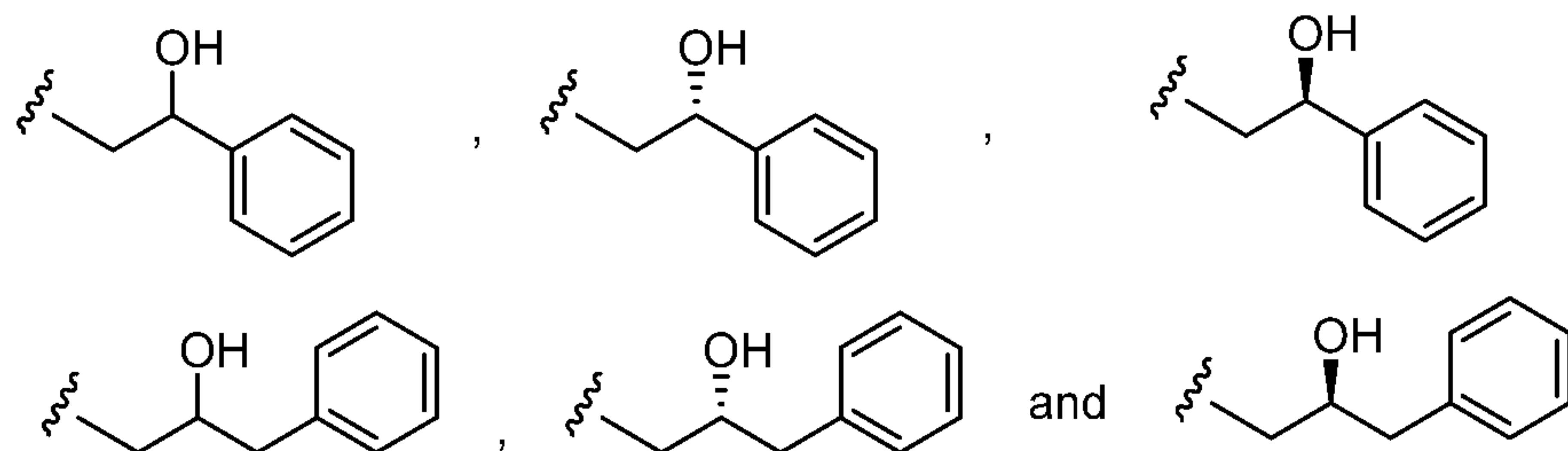
[0168] For the purpose of the present disclosure, the term "(amino)(heteroaryl)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one amino, alkylamino, or dialkylamino group and one optionally substituted heteroaryl group. In one embodiment, the alkyl is a C₁₋₆ alkyl. In one embodiment, the alkyl is a C₁₋₄ alkyl. In one embodiment, the optionally substituted heteroaryl group is an optionally substituted pyridyl. Non-limiting exemplary (amino)(heteroaryl)alkyl groups include:



[0169] For the purpose of the present disclosure, the term "(cycloalkyl)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one optionally substituted cycloalkyl group. In one embodiment, the alkyl is a C₁₋₄ alkyl. In one embodiment, the cycloalkyl is a C₃₋₆ cycloalkyl. In one embodiment, the optionally substituted cycloalkyl group is substituted with an amino or (amino)alkyl group. Non-limiting exemplary (cycloalkyl)alkyl groups include:



[0170] For the purpose of the present disclosure, the term "(hydroxy)(aryl)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one hydroxy group and one optionally substituted aryl group. In one embodiment, the alkyl is a C₁₋₆ alkyl. In one embodiment, the optionally substituted aryl group is an optionally substituted phenyl. Non-limiting exemplary (hydroxy)(aryl)alkyl groups include:



[0171] For the purpose of the present disclosure, the term "carboxamido" as used by itself or as part of another group refers to a radical of formula $\text{-C(=O)NR}^{26a}\text{R}^{26b}$, wherein R^{26a} and R^{26b} are each independently hydrogen, optionally substituted alkyl, optionally substituted aryl, aralkyl, (heteroaryl)alkyl, or optionally substituted heteroaryl, or R^{26a} and R^{26b} taken together with the nitrogen to which they are attached from a 3- to 8-membered heterocyclo group. In one embodiment, R^{26a} and R^{26b} are each independently hydrogen or optionally substituted alkyl. Non-limiting exemplary carboxamido groups include -CONH_2 , -CON(H)CH_3 , $\text{-CON(CH}_3)_2$, and -CON(H)Ph .

[0172] For the purpose of the present disclosure, the term "(carboxamido)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with a carboxamido group. Non-limiting exemplary (carboxamido)alkyl groups include $\text{-CH}_2\text{CONH}_2$, $\text{-C(H)CH}_3\text{-CONH}_2$, and $\text{-CH}_2\text{CON(H)CH}_3$.

[0173] For the purpose of the present disclosure, the term "sulfonamido" as used by itself or as part of another group refers to a radical of the formula $\text{-SO}_2\text{NR}^{27a}\text{R}^{27b}$, wherein R^{27a} and R^{27b} are each independently hydrogen, optionally substituted alkyl, or optionally substituted aryl, or R^{27a} and R^{27b} taken together with the nitrogen to which they are attached from a 3- to 8-membered heterocyclo group. Non-limiting exemplary sulfonamido groups include $\text{-SO}_2\text{NH}_2$, $\text{-SO}_2\text{N(H)CH}_3$, and $\text{-SO}_2\text{N(H)Ph}$.

[0174] For the purpose of the present disclosure, the term "alkylcarbonyl" as used by itself or as part of another group refers to a carbonyl group, *i.e.*, -C(=O)- , substituted by an alkyl group. A non-limiting exemplary alkylcarbonyl group is -COCH_3 .

[0175] For the purpose of the present disclosure, the term "arylcarbonyl" as used by itself or as part of another group refers to a carbonyl group, *i.e.*, -C(=O)- , substituted by an optionally substituted aryl group. A non-limiting exemplary arylcarbonyl group is -COPh .

[0176] For the purpose of the present disclosure, the term "alkylsulfonyl" as used by itself or as part of another group refers to a sulfonyl group, *i.e.*, $\text{-SO}_2\text{-}$, substituted by any

of the above-mentioned optionally substituted alkyl groups. A non-limiting exemplary alkylsulfonyl group is $-\text{SO}_2\text{CH}_3$.

[0177] For the purpose of the present disclosure, the term "arylsulfonyl" as used by itself or as part of another group refers to a sulfonyl group, *i.e.*, $-\text{SO}_2-$, substituted by any of the above-mentioned optionally substituted aryl groups. A non-limiting exemplary arylsulfonyl group is $-\text{SO}_2\text{Ph}$.

[0178] For the purpose of the present disclosure, the term "mercaptoalkyl" as used by itself or as part of another group refers to any of the above-mentioned alkyl groups substituted by a $-\text{SH}$ group.

[0179] For the purpose of the present disclosure, the term "carboxy" as used by itself or as part of another group refers to a radical of the formula $-\text{COOH}$.

[0180] For the purpose of the present disclosure, the term "carboxyalkyl" as used by itself or as part of another group refers to any of the above-mentioned alkyl groups substituted with a $-\text{COOH}$. A non-limiting exemplary carboxyalkyl group is $-\text{CH}_2\text{CO}_2\text{H}$.

[0181] For the purpose of the present disclosure, the term "alkoxycarbonyl" as used by itself or as part of another group refers to a carbonyl group, *i.e.*, $-\text{C}(=\text{O})-$, substituted by an alkoxy group. Non-limiting exemplary alkoxycarbonyl groups are $-\text{CO}_2\text{Me}$ and $-\text{CO}_2\text{Et}$.

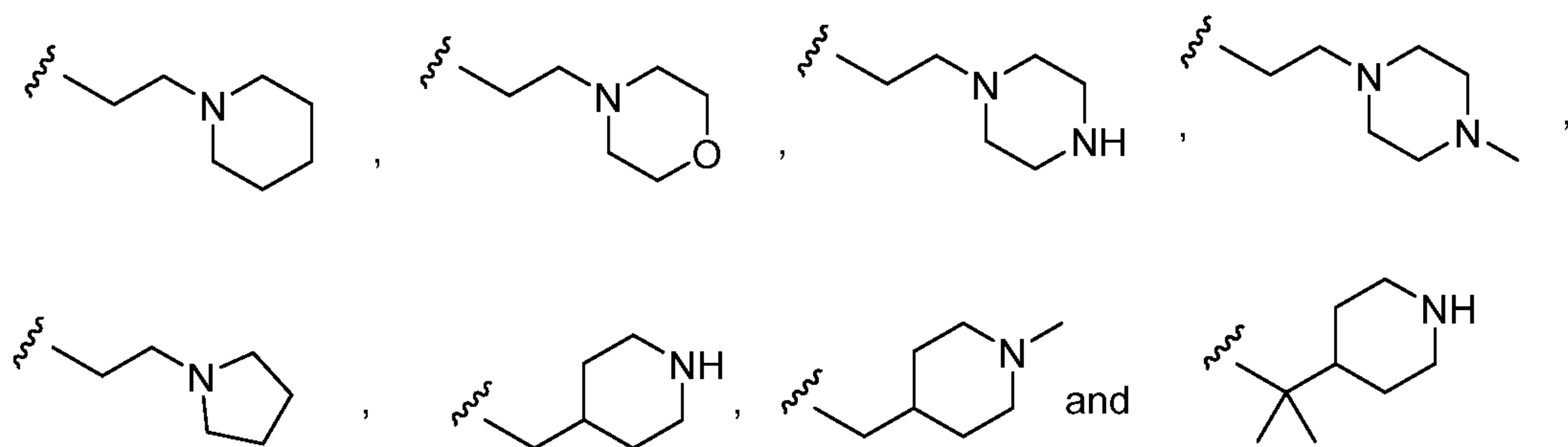
[0182] For the purpose of the present disclosure, the term "aralkyl" or "arylalkyl" as used by itself or as part of another group refers to an alkyl group substituted with one, two, or three optionally substituted aryl groups. In one embodiment, the aralkyl group is a C_{1-4} alkyl substituted with one optionally substituted aryl group. In another embodiment, the aralkyl group is a C_1 or C_2 alkyl substituted with one optionally substituted phenyl group. In another embodiment, the aralkyl group is a C_1 alkyl substituted with one optionally substituted phenyl group, *i.e.*, a benzyl group wherein the phenyl is optionally substituted. Non-limiting exemplary aralkyl groups include benzyl, phenethyl, $-\text{CHPh}_2$, $-\text{CH}_2(4\text{-OH-Ph})$, and $-\text{CH}(4\text{-F-Ph})_2$.

[0183] For the purpose of the present disclosure, the term "ureido" as used by itself or as part of another group refers to a radical of the formula $-\text{NR}^{30a}-\text{C}(=\text{O})-\text{NR}^{30b}\text{R}^{30c}$, wherein R^{22a} is hydrogen, alkyl, or optionally substituted aryl, and R^{30b} and R^{30c} are each independently hydrogen, alkyl, or optionally substituted aryl, or R^{30b} and R^{30c} taken together with the nitrogen to which they are attached form a 4- to 8-membered

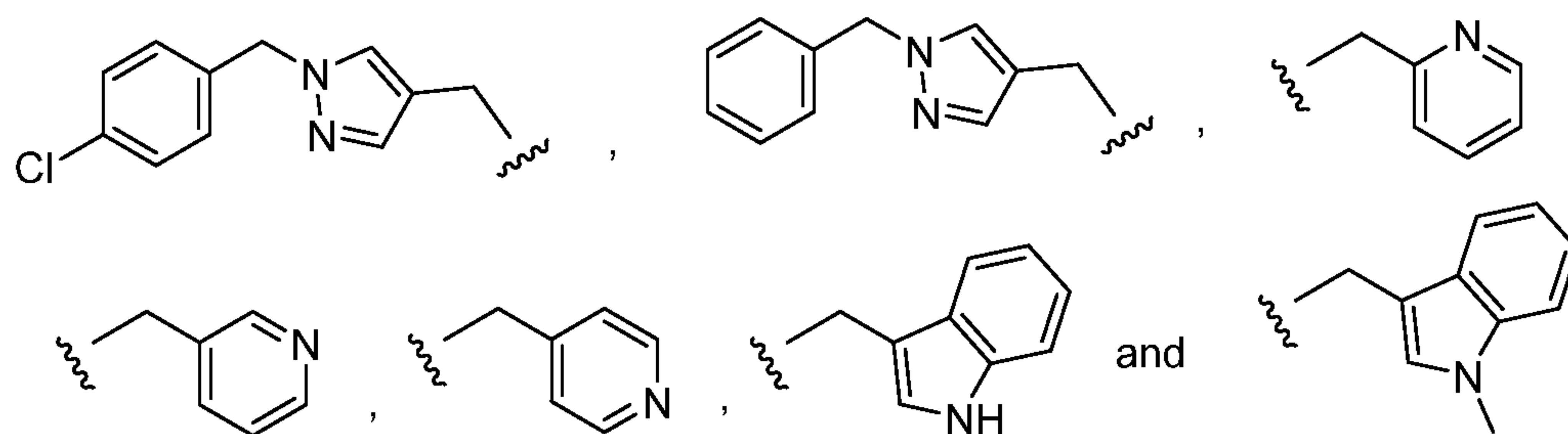
heterocyclo group. Non-limiting exemplary ureido groups include -NH-C(C=O)-NH_2 and -NH-C(C=O)-NHCH_3 .

[0184] For the purpose of the present disclosure, the term "guanidino" as used by itself or as part of another group refers to a radical of the formula $\text{-NR}^{28a}\text{-C(=NR}^{29}\text{)-NR}^{28b}\text{R}^{28c}$, wherein R^{28a} , R^{28b} , and R^{28c} are each independently hydrogen, alkyl, or optionally substituted aryl, and R^{29} is hydrogen, alkyl, cyano, alkylsulfonyl, alkylcarbonyl, carboxamido, or sulfonamido. Non-limiting exemplary guanidino groups include -NH-C(C=NH)-NH_2 , -NH-C(C=NCN)-NH_2 , and $\text{-NH-C(C=NH)-NHCH}_3$.

[0185] For the purpose of the present disclosure, the term "(heterocyclo)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one, two, or three optionally substituted heterocyclo groups. In one embodiment, the (heterocyclo)alkyl is a C_{1-4} alkyl substituted with one optionally substituted heterocyclo group. The heterocyclo can be linked to the alkyl group through a carbon or nitrogen atom. Non-limiting exemplary (heterocyclo)alkyl groups include:



[0186] For the purpose of the present disclosure, the term "(heteroaryl)alkyl" or "heteroaralkyl" as used by itself or as part of another group refers to an alkyl group substituted with one, two, or three optionally substituted heteroaryl groups. In one embodiment, the (heteroaryl)alkyl group is a C_{1-4} alkyl substituted with one optionally substituted heteroaryl group. Non-limiting exemplary (heteroaryl)alkyl groups include:



[0187] For the purpose of the present disclosure, the term "alkylcarbonylamino" as used by itself or as part of another group refers to an alkylcarbonyl group attached to an amino. A non-limiting exemplary alkylcarbonylamino group is -NHCOCH_3 .

[0188] The present disclosure encompasses any of the Compounds of the Disclosure being isotopically-labelled (*i.e.*, radiolabeled) by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H (or deuterium (D)), ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively, *e.g.*, ^3H , ^{11}C , and ^{14}C . In one embodiment, provided is a composition wherein substantially all of the atoms at a position within the Compound of the Disclosure are replaced by an atom having a different atomic mass or mass number. In another embodiment, provided is a composition wherein a portion of the atoms at a position within the Compound of the disclosure are replaced, *i.e.*, the Compound of the Disclosure is enriched at a position with an atom having a different atomic mass or mass number." Isotopically-labelled Compounds of the Disclosure can be prepared by methods known in the art.

[0189] Compounds of the Disclosure may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present disclosure is meant to encompass the use of all such possible forms, as well as their racemic and resolved forms and mixtures thereof. The individual enantiomers can be separated according to methods known in the art in view of the present disclosure. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that they include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present disclosure as well.

[0190] As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

[0191] The term "chiral center" or "asymmetric carbon atom" refers to a carbon atom to which four different groups are attached.

[0192] The terms "enantiomer" and "enantiomeric" refer to a molecule that cannot be superimposed on its mirror image and hence is optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image compound rotates the plane of polarized light in the opposite direction.

- [0193] The term "racemic" refers to a mixture of equal parts of enantiomers and which mixture is optically inactive.
- [0194] The term "absolute configuration" refers to the spatial arrangement of the atoms of a chiral molecular entity (or group) and its stereochemical description, *e.g.*, R or S.
- [0195] The stereochemical terms and conventions used in the specification are meant to be consistent with those described in *Pure & Appl. Chem* 68:2193 (1996), unless otherwise indicated.
- [0196] The term "enantiomeric excess" or "ee" refers to a measure for how much of one enantiomer is present compared to the other. For a mixture of *R* and *S* enantiomers, the percent enantiomeric excess is defined as $|R - S| * 100$, where *R* and *S* are the respective mole or weight fractions of enantiomers in a mixture such that $R + S = 1$. With knowledge of the optical rotation of a chiral substance, the percent enantiomeric excess is defined as $([\alpha]_{\text{obs}}/[\alpha]_{\text{max}})*100$, where $[\alpha]_{\text{obs}}$ is the optical rotation of the mixture of enantiomers and $[\alpha]_{\text{max}}$ is the optical rotation of the pure enantiomer. Determination of enantiomeric excess is possible using a variety of analytical techniques, including NMR spectroscopy, chiral column chromatography or optical polarimetry.
- [0197] The terms "enantiomerically pure" or "enantiopure" refer to a sample of a chiral substance all of whose molecules (within the limits of detection) have the same chirality sense.
- [0198] The terms "enantiomerically enriched" or "enantioenriched" refer to a sample of a chiral substance whose enantiomeric ratio is greater than 50:50. Enantiomerically enriched compounds may be enantiomerically pure.
- [0199] The terms "a" and "an" refer to one or more.
- [0200] The term "about," as used herein, includes the recited number $\pm 10\%$. Thus, "about 10" means 9 to 11.
- [0201] The present disclosure encompasses the preparation and use of salts of the Compounds of the Disclosure, including non-toxic pharmaceutically acceptable salts. Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts and basic salts. The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, cesium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the

like; inorganic acid salts such as hydrochloride, hydrobromide, phosphate, sulphate and the like; organic acid salts such as citrate, lactate, tartrate, maleate, fumarate, mandelate, acetate, dichloroacetate, trifluoroacetate, oxalate, formate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate and the like; and amino acid salts such as arginate, asparinate, glutamate and the like. The term "pharmaceutically acceptable salt" as used herein, refers to any salt, *e.g.*, obtained by reaction with an acid or a base, of a Compound of the Disclosure that is physiologically tolerated in the target patient (*e.g.*, a mammal, *e.g.*, a human).

[0202] Acid addition salts can be formed by mixing a solution of the particular Compound of the Disclosure with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid, oxalic acid, dichloroacetic acid, or the like. Basic salts can be formed by mixing a solution of the compound of the present disclosure with a solution of a pharmaceutically acceptable non-toxic base such as sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate and the like.

[0203] The present disclosure encompasses the preparation and use of solvates of Compounds of the Disclosure. Solvates typically do not significantly alter the physiological activity or toxicity of the compounds, and as such may function as pharmacological equivalents. The term "solvate" as used herein is a combination, physical association and/or solvation of a compound of the present disclosure with a solvent molecule such as, *e.g.* a disolvate, monosolvate or hemisolvate, where the ratio of solvent molecule to compound of the present disclosure is about 2:1, about 1:1 or about 1:2, respectively. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate can be isolated, such as when one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid. Thus, "solvate" encompasses both solution-phase and isolatable solvates. Compounds of the Disclosure can be present as solvated forms with a pharmaceutically acceptable solvent, such as water, methanol, ethanol, and the like, and it is intended that the disclosure includes both solvated and unsolvated forms of Compounds of the Disclosure. One type of solvate is a hydrate. A "hydrate" relates to a particular subgroup of solvates where the solvent molecule is water. Solvates typically can function as pharmacological equivalents. Preparation of solvates is known in the art.

See, for example, M. Caira *et al*, *J. Pharmaceut. Sci.*, 93(3):601-611 (2004), which describes the preparation of solvates of fluconazole with ethyl acetate and with water. Similar preparation of solvates, hemisolvates, hydrates, and the like are described by E.C. van Tonder *et al.*, *AAPS Pharm. Sci. Tech.*, 5(1):Article 12 (2004), and A.L. Bingham *et al.*, *Chem. Commun.* 603-604 (2001). A typical, non-limiting, process of preparing a solvate would involve dissolving a Compound of the Disclosure in a desired solvent (organic, water, or a mixture thereof) at temperatures above 20°C to about 25°C, then cooling the solution at a rate sufficient to form crystals, and isolating the crystals by known methods, *e.g.*, filtration. Analytical techniques such as infrared spectroscopy can be used to confirm the presence of the solvent in a crystal of the solvate.

[0204] Since Compounds of the Disclosure are inhibitors of SMYD proteins, such as SMYD3 and SMYD2, a number of diseases, conditions, or disorders mediated by SMYD proteins, such as SMYD3 and SMYD2, can be treated by employing these compounds. The present disclosure is thus directed generally to a method for treating a disease, condition, or disorder responsive to the inhibition of SMYD proteins, such as SMYD3 and SMYD2, in an animal suffering from, or at risk of suffering from, the disorder, the method comprising administering to the animal an effective amount of one or more Compounds of the Disclosure.

[0205] The present disclosure is further directed to a method of inhibiting SMYD proteins in an animal in need thereof, the method comprising administering to the animal a therapeutically effective amount of at least one Compound of the Disclosure.

[0206] The present disclosure is further directed to a method of inhibiting SMYD3 in an animal in need thereof, the method comprising administering to the animal a therapeutically effective amount of at least one Compound of the Disclosure.

[0207] The present disclosure is further directed to a method of inhibiting SMYD2 in an animal in need thereof, the method comprising administering to the animal a therapeutically effective amount of at least one Compound of the Disclosure.

[0208] As used herein, the terms "treat," "treating," "treatment," and the like refer to eliminating, reducing, or ameliorating a disease or condition, and/or symptoms associated therewith. Although not precluded, treating a disease or condition does not require that the disease, condition, or symptoms associated therewith be completely eliminated. As used herein, the terms "treat," "treating," "treatment," and the like may include "prophylactic treatment," which refers to reducing the probability of redeveloping a

disease or condition, or of a recurrence of a previously-controlled disease or condition, in a subject who does not have, but is at risk of or is susceptible to, redeveloping a disease or condition or a recurrence of the disease or condition. The term "treat" and synonyms contemplate administering a therapeutically effective amount of a Compound of the Disclosure to an individual in need of such treatment.

[0209] Within the meaning of the disclosure, "treatment" also includes relapse prophylaxis or phase prophylaxis, as well as the treatment of acute or chronic signs, symptoms and/or malfunctions. The treatment can be orientated symptomatically, for example, to suppress symptoms. It can be effected over a short period, be oriented over a medium term, or can be a long-term treatment, for example within the context of a maintenance therapy.

[0210] The term "therapeutically effective amount" or "effective dose" as used herein refers to an amount of the active ingredient(s) that is(are) sufficient, when administered by a method of the disclosure, to efficaciously deliver the active ingredient(s) for the treatment of condition or disease of interest to an individual in need thereof. In the case of a cancer or other proliferation disorder, the therapeutically effective amount of the agent may reduce (*i.e.*, retard to some extent and preferably stop) unwanted cellular proliferation; reduce the number of cancer cells; reduce the tumor size; inhibit (*i.e.*, retard to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (*i.e.*, retard to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; modulate protein methylation in the target cells; and/or relieve, to some extent, one or more of the symptoms associated with the cancer. To the extent the administered compound or composition prevents growth and/or kills existing cancer cells, it may be cytostatic and/or cytotoxic.

[0211] The term "container" means any receptacle and closure therefore suitable for storing, shipping, dispensing, and/or handling a pharmaceutical product.

[0212] The term "insert" means information accompanying a pharmaceutical product that provides a description of how to administer the product, along with the safety and efficacy data required to allow the physician, pharmacist, and patient to make an informed decision regarding use of the product. The package insert generally is regarded as the "label" for a pharmaceutical product.

[0213] The term "disease" or "condition" or "disorder" denotes disturbances and/or anomalies that as a rule are regarded as being pathological conditions or functions, and

that can manifest themselves in the form of particular signs, symptoms, and/or malfunctions. As demonstrated below, Compounds of the Disclosure inhibit SMYD proteins, such as SMYD3 and SMYD2 and can be used in treating diseases and conditions such as proliferative diseases, wherein inhibition of SMYD proteins, such as SMYD3 and SMYD2 provides a benefit.

[0214] In some embodiments, the Compounds of the Disclosure can be used to treat a "SMYD protein mediated disorder" (*e.g.*, a SMYD3-mediated disorder or a SMYD2-mediated disorder). A SMYD protein mediated disorder is any pathological condition in which a SMYD protein is known to play a role. In some embodiments, a SMYD-mediated disorder is a proliferative disease.

[0215] In some embodiments inhibiting SMYD proteins, such as SMYD3 and SMYD2, is the inhibition of the activity of one or more activities of SMYD proteins such as SMYD3 and SMYD2. In some embodiments, the activity of the SMYD proteins such as SMYD3 and SMYD2 is the ability of the SMYD protein such as SMYD3 or SMYD2 to transfer a methyl group to a target protein (*e.g.*, histone). It should be appreciated that the activity of the one or more SMYD proteins such as SMYD3 and SMYD2 may be inhibited *in vitro* or *in vivo*. Exemplary levels of inhibition of the activity one or more SMYD proteins such as SMYD3 and SMYD2 include at least 10% inhibition, at least 20% inhibition, at least 30% inhibition, at least 40% inhibition, at least 50% inhibition, at least 60% inhibition, at least 70% inhibition, at least 80% inhibition, at least 90% inhibition, and up to 100% inhibition.

[0216] The SMYD (SET and MYND domain) family of lysine methyltransferases (KMTs) plays pivotal roles in various cellular processes, including gene expression regulation and DNA damage response. The family of human SMYD proteins consists of SMYD1, SMYD2, SMYD3, SMYD4 and SMYD5. SMYD1, SMYD2, and SMYD3 share a high degree of sequence homology and, with the exception of SMYD5, human SMYD proteins harbor at least one C-terminal tetratricopeptide repeat (TPR) domain. (See *e.g.*, Abu-Farha et al. *J Mol Cell Biol* (2011) 3 (5) 301-308). The SMYD proteins have been found to be linked to various cancers (See *e.g.*, Hamamoto et al. *Nat Cell Biol.* 2004, 6: 731-740), Hu et al. *Cancer Research* 2009, 4067-4072, and Komatsu et al. *Carcinogenesis* 2009, 30:1139-1146.)

[0217] SMYD3 is a protein methyltransferase found to be expressed at high levels in a number of different cancers (Hamamoto, R., *et al.*, *Nat. Cell Biol.*, 6(8):731-40 (2004)).

SMYD3 likely plays a role in the regulation of gene transcription and signal transduction pathways critical for survival of breast, liver, prostate and lung cancer cell lines (Hamamoto, R., *et al.*, *Nat. Cell Biol.*, 6(8):731-40 (2004); Hamamoto, R., *et al.*, *Cancer Sci.*, 97(2):113-8 (2006); Van Aller, G.S., *et al.*, *Epigenetics*, 7(4):340-3 (2012); Liu, C., *et al.*, *J. Natl. Cancer Inst.*, 105(22):1719-28 (2013); Mazur, P.K., *et al.*, *Nature*, 510(7504):283-7 (2014)).

[0218] Genetic knockdown of SMYD3 leads to a decrease in proliferation of a variety of cancer cell lines (Hamamoto, R., *et al.*, *Nat. Cell Biol.*, 6(8):731-40 (2004); Hamamoto, R., *et al.*, *Cancer Sci.*, 97(2):113-8 (2006); Van Aller, G.S., *et al.*, *Epigenetics*, 7(4):340-3 (2012); Liu, C., *et al.*, *J. Natl. Cancer Inst.*, 105(22):1719-28 (2013); Mazur, P.K., *et al.*, *Nature*, 510(7504):283-7 (2014)). Several studies employing RNAi-based technologies have shown that ablation of SMYD3 in hepatocellular carcinoma cell lines greatly reduces cell viability and that its pro-survival role is dependent on its catalytic activity (Hamamoto, R., *et al.*, *Nat. Cell Biol.*, 6(8):731-40 (2004); Van Aller, G.S., *et al.*, *Epigenetics*, 7(4):340-3 (2012)). Moreover, SMYD3 has also been shown to be a critical mediator of transformation resulting from gain of function mutations in the oncogene, KRAS for both pancreatic and lung adenocarcinoma in mouse models. The dependence of KRAS on SMYD3 was also shown to be dependent on its catalytic activity (Mazur, P.K., *et al.*, *Nature*, 510(7504):283-7 (2014)). SMYD3 function has also been implicated in colorectal cancers and RNAi mediated knockdown of SMYD3 has been shown to impair colorectal cell proliferation. (Peserico *et al.*, *Cell Physiol.* 2015 Feb 28. doi: 10.1002/jcp.24975. [Epub ahead of print]).

[0219] Furthermore, SMYD3 function has also been shown to play a role in immunology and development. For instance, de Almeida reported that SMYD3 plays a role in generation of inducible regulatory T cells (iTreg) cells. In a mouse model of respiratory syncytial virus (RSV) infection, a model in which iTreg cells have a critical role in regulating lung pathogenesis, SMYD3^{-/-} mice demonstrated exacerbation of RSV-induced disease related to enhanced proinflammatory responses and worsened pathogenesis within the lung (de Almeida *et al.* *Mucosal Immunol.* 2015 Feb 11. doi: 10.1038/mi.2015.4. [Epub ahead of print]). In addition, as to development, Proserpio *et al.* have shown the importance of SMYD3 in the regulation of skeletal muscle atrophy (Proserpio *et al.* *Genes Dev.* 2013 Jun 1;27(11):1299-312), while Fujii *et al.* have

elucidated the role of SMYD3 in cardiac and skeletal muscle development (Fujii et al. *PLoS One*. 2011;6(8):e23491).

[0220] SMYD2 (SET and MYND domain-containing protein 2) was first characterized as protein that is a member of a sub-family of SET domain containing proteins which catalyze the site-specific transfer of methyl groups onto substrate proteins. SMYD2 was initially shown to have methyltransferase activity towards lysine 36 on histone H3 (H3K36) but has subsequently been shown to have both histone and non-histone methyltransferase activity.

[0221] SMYD2 has been implicated in the pathogenesis of multiple cancers. It has been shown to be over-expressed, compared to matched normal samples, in tumors of the breast, cervix, colon, kidney, liver, head and neck, skin, pancreas, ovary, esophagus and prostate, as well as hematologic malignancies such as AML, B- and T-ALL, CLL and MCL, suggesting a role for SMYD2 in the biology of these cancers. More specifically, studies using genetic knock-down of SMYD2 have demonstrated anti-proliferative effects in esophageal squamous cell carcinoma (ESCC), bladder carcinoma and cervical carcinoma cell lines. (See *e.g.*, Komatsu et al., *Carcinogenesis* 2009, 30, 1139, and Cho et al., *Neoplasia*. 2012 Jun;14(6):476-86). Moreover, high expression of SMYD2 has been shown to be a poor prognostic factor in both ESCC and pediatric ALL. (See *e.g.*, Komatsu et al. *Br J Cancer*. 2015 Jan 20;112(2):357-64, and Sakamoto et al., *Leuk Res*. 2014 Apr;38(4):496-502). Recently, Nguyen et al., have shown that a small molecule inhibitor of SMYD2 (LLY-507) inhibited the proliferation of several esophageal, liver and breast cancer cell lines in a dose-dependent manner. (Nguyen et al. *J Biol Chem*. 2015 Mar 30. pii: jbc.M114.626861. [Epub ahead of print]).

[0222] SMYD2 has also been implicated in immunology. For instance, Xu et al. have shown that SMYD2 is a negative regulator of macrophage activation by suppressing Interleukin-6 and TNF-alpha production. (Xu et al., *J Biol Chem*. 2015 Feb 27;290(9):5414-23).

[0223] In one aspect, the present disclosure provides a method of treating cancer in a patient comprising administering a therapeutically effective amount of a Compound of the Disclosure. While not being limited to a specific mechanism, in some embodiments, Compounds of the Disclosure can treat cancer by inhibiting SMYD proteins, such as SMYD3 and SMYD2. Examples of treatable cancers include, but are not limited to, adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma,

acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast,

medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

[0224] In another embodiment, the cancer is breast, cervix, colon, kidney, liver, head and neck, skin, pancreas, ovary, esophagus, or prostate cancer.

[0225] In another embodiment, the cancer is a hematologic malignancy such as acute myeloid leukemia (AML), B- and T-acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), or mantle cell lymphoma (MCL).

[0226] In another embodiment, the cancer is esophageal squamous cell carcinoma (ESCC), bladder carcinoma, or cervical carcinoma.

[0227] In another embodiment, the cancer is a leukemia, for example a leukemia selected from acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia and mixed lineage leukemia (MLL). In another embodiment the cancer is NUT-midline carcinoma. In another embodiment the cancer is

multiple myeloma. In another embodiment the cancer is a lung cancer such as small cell lung cancer (SCLC). In another embodiment the cancer is a neuroblastoma. In another embodiment the cancer is Burkitt's lymphoma. In another embodiment the cancer is cervical cancer. In another embodiment the cancer is esophageal cancer. In another embodiment the cancer is ovarian cancer. In another embodiment the cancer is colorectal cancer. In another embodiment, the cancer is prostate cancer. In another embodiment, the cancer is breast cancer.

[0228] In another embodiment, the present disclosure provides a therapeutic method of modulating protein methylation, gene expression, cell proliferation, cell differentiation and/or apoptosis *in vivo* in the cancers mentioned above by administering a therapeutically effective amount of a Compound of the Disclosure to a subject in need of such therapy.

[0229] Compounds of the Disclosure can be administered to a mammal in the form of a raw chemical without any other components present. Compounds of the Disclosure can also be administered to a mammal as part of a pharmaceutical composition containing the compound combined with a suitable pharmaceutically acceptable carrier. Such a carrier can be selected from pharmaceutically acceptable excipients and auxiliaries. The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable vehicle" encompasses any of the standard pharmaceutical carriers, solvents, surfactants, or vehicles. Suitable pharmaceutically acceptable vehicles include aqueous vehicles and nonaqueous vehicles. Standard pharmaceutical carriers and their formulations are described in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, 19th ed. 1995.

[0230] Pharmaceutical compositions within the scope of the present disclosure include all compositions where a Compound of the Disclosure is combined with one or more pharmaceutically acceptable carriers. In one embodiment, the Compound of the Disclosure is present in the composition in an amount that is effective to achieve its intended therapeutic purpose. While individual needs may vary, a determination of optimal ranges of effective amounts of each compound is within the skill of the art. Typically, a Compound of the Disclosure can be administered to a mammal, *e.g.*, a human, orally at a dose of from about 0.0025 to about 1500 mg per kg body weight of the mammal, or an equivalent amount of a pharmaceutically acceptable salt or solvate thereof, per day to treat the particular disorder. A useful oral dose of a Compound of the

Disclosure administered to a mammal is from about 0.0025 to about 50 mg per kg body weight of the mammal, or an equivalent amount of the pharmaceutically acceptable salt or solvate thereof. For intramuscular injection, the dose is typically about one-half of the oral dose.

[0231] A unit oral dose may comprise from about 0.01 mg to about 1 g of the Compound of the Disclosure, *e.g.*, about 0.01 mg to about 500 mg, about 0.01 mg to about 250 mg, about 0.01 mg to about 100 mg, 0.01 mg to about 50 mg, *e.g.*, about 0.1 mg to about 10 mg, of the compound. The unit dose can be administered one or more times daily, *e.g.*, as one or more tablets or capsules, each containing from about 0.01 mg to about 1 g of the compound, or an equivalent amount of a pharmaceutically acceptable salt or solvate thereof.

[0232] A pharmaceutical composition of the present disclosure can be administered to any patient that may experience the beneficial effects of a Compound of the Disclosure. Foremost among such patients are mammals, *e.g.*, humans and companion animals, although the disclosure is not intended to be so limited. In one embodiment, the patient is a human.

[0233] A pharmaceutical composition of the present disclosure can be administered by any means that achieves its intended purpose. For example, administration can be by the oral, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, intranasal, transmucosal, rectal, intravaginal or buccal route, or by inhalation. The dosage administered and route of administration will vary, depending upon the circumstances of the particular subject, and taking into account such factors as age, gender, health, and weight of the recipient, condition or disorder to be treated, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

[0234] In one embodiment, a pharmaceutical composition of the present disclosure can be administered orally. In another embodiment, a pharmaceutical composition of the present disclosure can be administered orally and is formulated into tablets, dragees, capsules, or an oral liquid preparation. In one embodiment, the oral formulation comprises extruded multiparticulates comprising the Compound of the Disclosure.

[0235] Alternatively, a pharmaceutical composition of the present disclosure can be administered rectally, and is formulated in suppositories.

[0236] Alternatively, a pharmaceutical composition of the present disclosure can be administered by injection.

- [0237] Alternatively, a pharmaceutical composition of the present disclosure can be administered transdermally.
- [0238] Alternatively, a pharmaceutical composition of the present disclosure can be administered by inhalation or by intranasal or transmucosal administration.
- [0239] Alternatively, a pharmaceutical composition of the present disclosure can be administered by the intravaginal route.
- [0240] A pharmaceutical composition of the present disclosure can contain from about 0.01 to 99 percent by weight, *e.g.*, from about 0.25 to 75 percent by weight, of a Compound of the Disclosure, *e.g.*, about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, or about 75% by weight of a Compound of the Disclosure.
- [0241] A pharmaceutical composition of the present disclosure is manufactured in a manner which itself will be known in view of the instant disclosure, for example, by means of conventional mixing, granulating, dragee-making, dissolving, extrusion, or lyophilizing processes. Thus, pharmaceutical compositions for oral use can be obtained by combining the active compound with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.
- [0242] Suitable excipients include fillers such as saccharides (for example, lactose, sucrose, mannitol or sorbitol), cellulose preparations, calcium phosphates (for example, tricalcium phosphate or calcium hydrogen phosphate), as well as binders such as starch paste (using, for example, maize starch, wheat starch, rice starch, or potato starch), gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, one or more disintegrating agents can be added, such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate.
- [0243] Auxiliaries are typically flow-regulating agents and lubricants such as, for example, silica, talc, stearic acid or salts thereof (*e.g.*, magnesium stearate or calcium stearate), and polyethylene glycol. Dragee cores are provided with suitable coatings that are resistant to gastric juices. For this purpose, concentrated saccharide solutions can be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene

glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate can be used. Dye stuffs or pigments can be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

[0244] Examples of other pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, or soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain a compound in the form of granules, which can be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers, or in the form of extruded multiparticulates. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils or liquid paraffin. In addition, stabilizers can be added.

[0245] Possible pharmaceutical preparations for rectal administration include, for example, suppositories, which consist of a combination of one or more active compounds with a suppository base. Suitable suppository bases include natural and synthetic triglycerides, and paraffin hydrocarbons, among others. It is also possible to use gelatin rectal capsules consisting of a combination of active compound with a base material such as, for example, a liquid triglyceride, polyethylene glycol, or paraffin hydrocarbon.

[0246] Suitable formulations for parenteral administration include aqueous solutions of the active compound in a water-soluble form such as, for example, a water-soluble salt, alkaline solution, or acidic solution. Alternatively, a suspension of the active compound can be prepared as an oily suspension. Suitable lipophilic solvents or vehicles for such as suspension may include fatty oils (for example, sesame oil), synthetic fatty acid esters (for example, ethyl oleate), triglycerides, or a polyethylene glycol such as polyethylene glycol-400 (PEG-400). An aqueous suspension may contain one or more substances to increase the viscosity of the suspension, including, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. The suspension may optionally contain stabilizers.

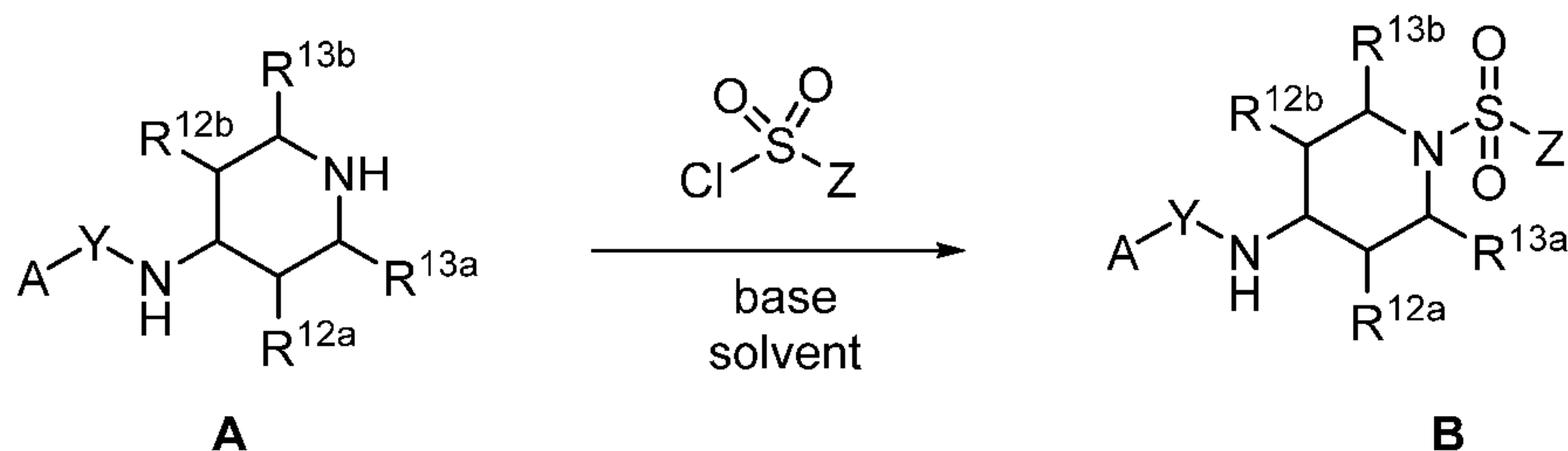
[0247] In another embodiment, the present disclosure provides kits which comprise a Compound of the Disclosure (or a composition comprising a Compound of the Disclosure) packaged in a manner that facilitates their use to practice methods of the present disclosure. In one embodiment, the kit includes a Compound of the Disclosure

(or a composition comprising a Compound of the Disclosure) packaged in a container, such as a sealed bottle or vessel, with a label affixed to the container or included in the kit that describes use of the compound or composition to practice the method of the disclosure. In one embodiment, the compound or composition is packaged in a unit dosage form. The kit further can include a device suitable for administering the composition according to the intended route of administration.

General Synthesis of Compounds

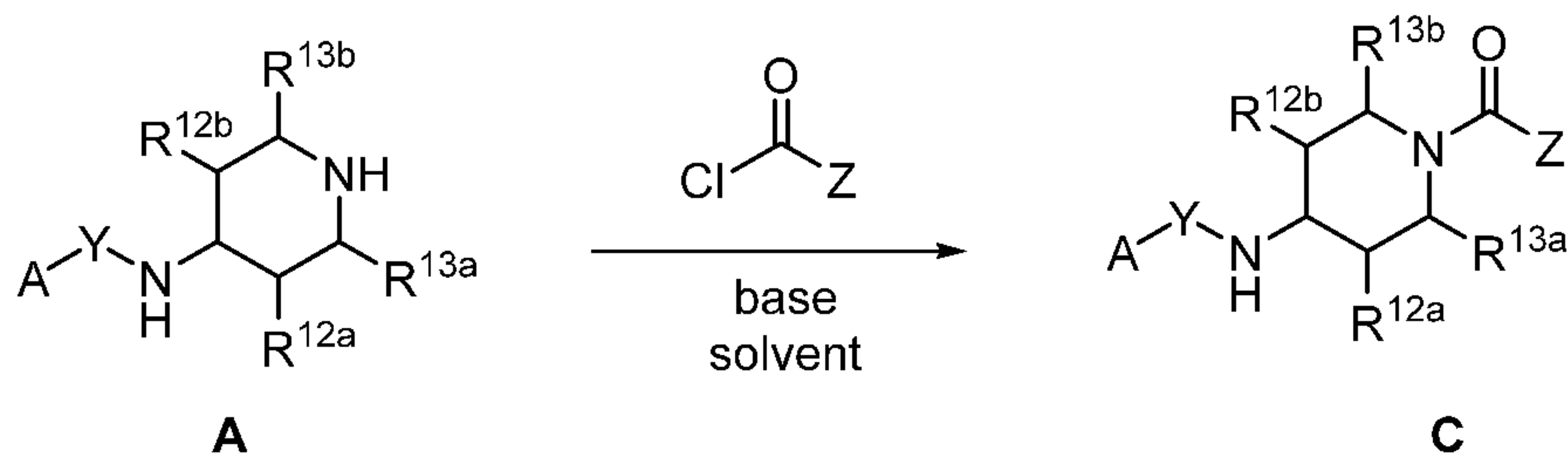
[0248] Compounds of the Disclosure are prepared using methods known to those skilled in the art in view of this disclosure, or by the illustrative methods shown in the General Schemes below. In the General Schemes, A, Y, R^{12a}, R^{12b}, R^{13a}, R^{13b}, and Z of Formulae **A-D** are as defined in connection with Formula **VI**, unless otherwise indicated. In any of the General Schemes, suitable protecting can be employed in the synthesis, for example, when Z is (amino)alkyl or any other group that may require protection. (See, Wuts, P. G. M.; Greene, T. W., "Greene's Protective Groups in Organic Synthesis", 4th Ed., J. Wiley & Sons, NY, 2007).

General Scheme 1

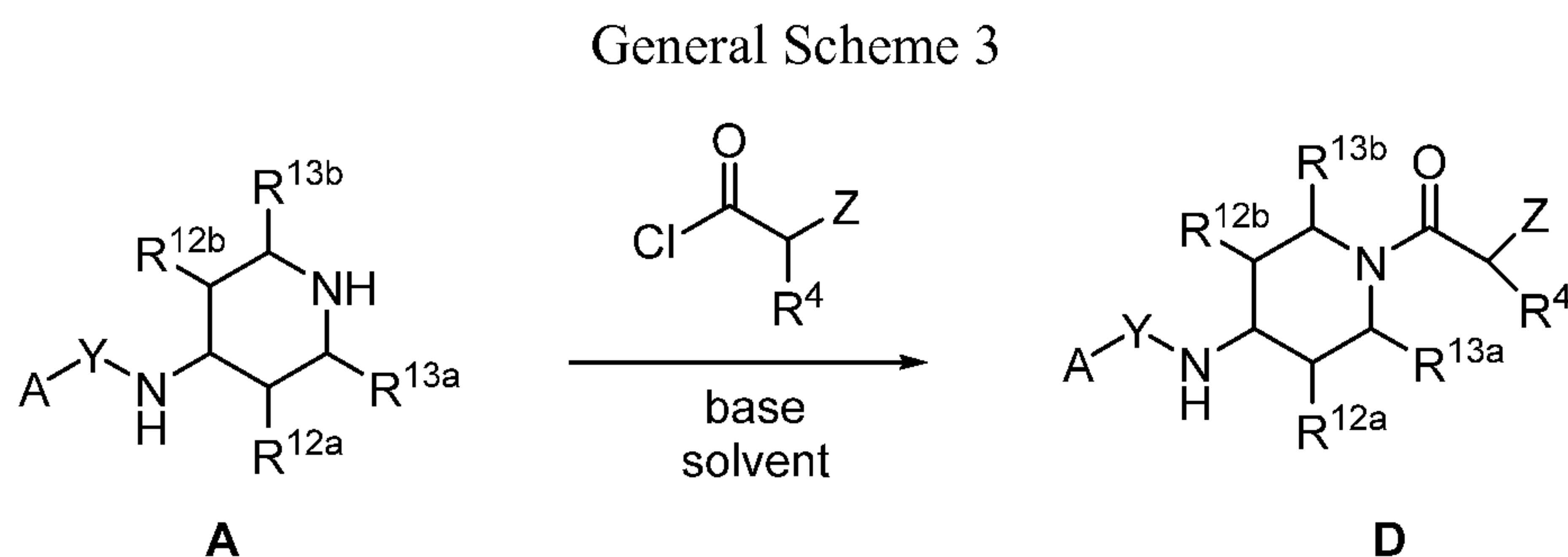


[0249] Compound A is converted to compound B (i.e., a compound having Formula **VI**, wherein X is -S(=O)₂-) by coupling with a suitable sulfonyl chloride (Z-SO₂Cl) in the presence of a suitable base such as TEA or DIPEA in a suitable solvent such as dichloromethane, acetonitrile, or DMF.

General Scheme 2



- [0250] Compound A is converted to compound C (i.e, a compound having Formula VI, wherein X is -C(=O)-) by coupling with a suitable acid chloride (Z-COCl) in the presence of a suitable base such as TEA or DIPEA in a suitable solvent such as dichloromethane, acetonitrile, or DMF, or by coupling with a suitable carboxylic acid (Z-CO₂H) in the presence of a suitable coupling reagent such as HATU and a suitable base such as TEA or DIPEA in a suitable solvent such as dichloromethane, acetonitrile, or DMF.



- [0251] Compound A is converted to compound D (i.e, a compound having Formula VI, wherein X is -C(=O)C(R⁴)(H)-) by coupling with a suitable carboxylic acid (Z-C(H)R⁴CO₂H) in the presence of a suitable coupling reagent such as HATU and a suitable base such as TEA or DIPEA in a suitable solvent such as dichloromethane, acetonitrile, or DMF.

EXAMPLES

General Synthetic Methods

- [0252] General methods and experimental procedures for preparing and characterizing Compounds of the Disclosure are set forth in the general schemes above and the examples below. Wherever needed, reactions were heated using conventional hotplate apparatus or heating mantle or microwave irradiation equipment. Reactions were conducted with or without stirring, under atmospheric or elevated pressure in either open or closed vessels. Reaction progress was monitored using conventional techniques such as TLC, HPLC, UPLC, or LCMS using instrumentation and methods described below. Reactions were quenched and crude compounds isolated using conventional methods as described in the specific examples provided. Solvent removal was carried out with or

without heating, under atmospheric or reduced pressure, using either a rotary or centrifugal evaporator.

[0253] Compound purification was carried out as needed using a variety of traditional methods including, but not limited to, preparative chromatography under acidic, neutral, or basic conditions using either normal phase or reverse phase HPLC or flash columns or Prep-TLC plates. Compound purity and mass confirmations were conducted using standard HPLC and / or UPLC and / or MS spectrometers and / or LCMS and / or GC equipment (*i.e.*, including, but not limited to the following instrumentation: Waters Alliance 2695 with 2996 PDA detector connected with ZQ detector and ESI source; Shimadzu LDMS-2020; Waters Acquity H Class with PDA detector connected with SQ detector and ESI source; Agilent 1100 Series with PDA detector; Waters Alliance 2695 with 2998 PDA detector; AB SCIEX API 2000 with ESI source; Agilent 7890 GC). Exemplified compounds were dissolved in either MeOH or MeCN to a concentration of approximately 1 mg/mL and analyzed by injection of 0.5-10 μ L into an appropriate LCMS system using the methods provided in the following table. In each case the flow rate is 1 ml/min.

Method	Column	Mobile Phase A	Mobile Phase B	Gradient Profile	MS Heat Block Temp (°C)	MS Detector Voltage (kV)
A	Shim-pack XR-ODS 2.2 μ m 3.0x50mm	Water/ 0.05% TFA	ACN /0.05% TFA	5% to 100% B in 2.0 minutes, 100% B for 1.1 minutes, 100% to 5% B in 0.2 minutes, then stop	250	1.5
B	Gemini-NX 3 μ m C18 110A	Water / 0.04% Ammonia	ACN	5% to 100% B in 2.0 minutes, 100% B for 1.1 minutes, 100% to 5% B in 0.1 minutes, then stop	200	0.75
C	Shim-pack XR-ODS 1.6 μ m 2.0x50mm	Water/ 0.05% TFA	ACN/ 0.05% TFA	5% to 100% B in 2.0 minutes, 100% B for 1.1 minutes, 100% to 5% B in 0.1 minutes, then stop	250	0.85

D	Shim-pack XR-ODS 2.2 μ m 3.0x50mm	Water/ 0.05% TFA	ACN/ 0.05% TFA	5% to 100% B in 2.0 minutes, 100% B for 1.1 minutes, 100% to 5% B in 0.1 minutes, then stop	250	0.95

[0254] Compound structure confirmations were carried out using standard 300 or 400 MHz NMR spectrometers with nOe's conducted whenever necessary.

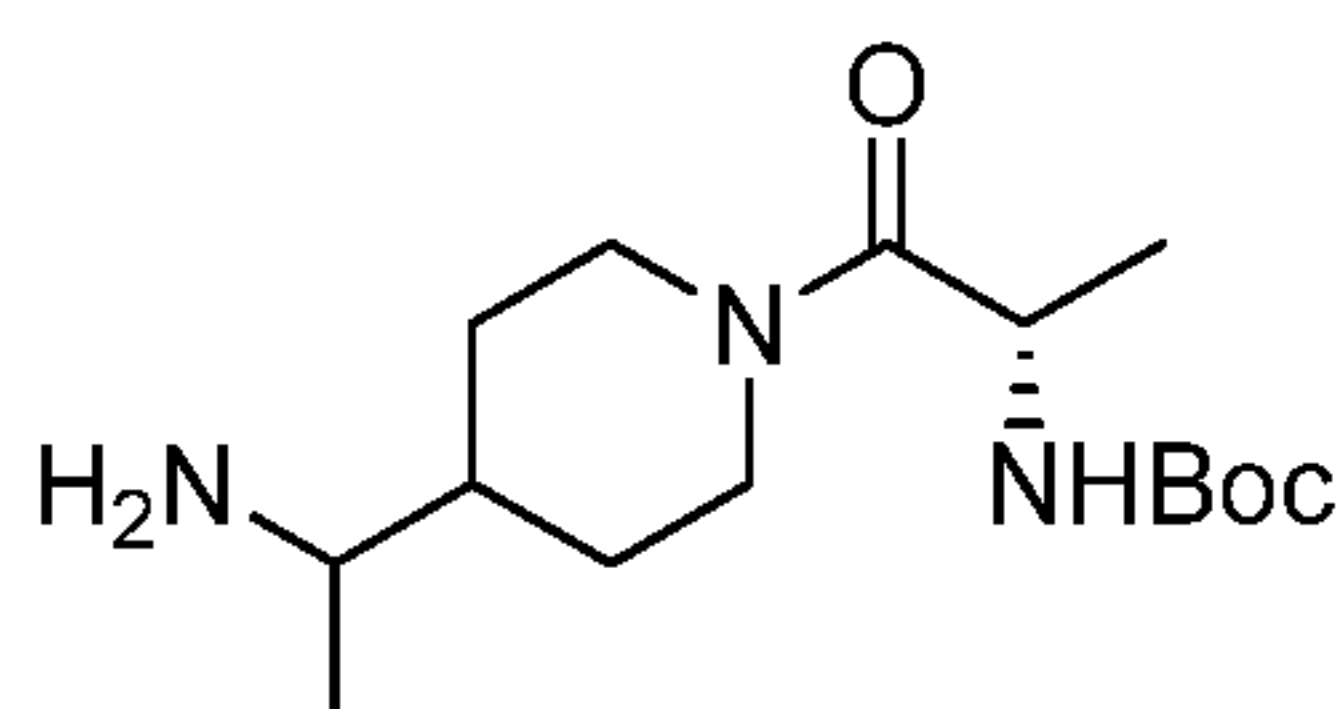
[0255] The following abbreviations are used herein:

Abbreviation	Meaning
ACN	acetonitrile
atm.	atmosphere
DCM	dichloromethane
DHP	dihydropyran
DIBAL	diisobutyl aluminum hydride
DIEA	diisopropyl ethylamine
DMF	dimethyl formamide
DMF-DMA	dimethyl formamide dimethyl acetal
DMSO	dimethyl sulfoxide
Dppf	1,1'-bis(diphenylphosphino)ferrocene
EA	ethyl acetate
ESI	electrospray ionization
EtOH	Ethanol
FA	formic acid
GC	gas chromatography
H	hour
Hex	hexanes
HMDS	hexamethyl disilazide
HPLC	high performance liquid chromatography
IPA	Isopropanol
LCMS	liquid chromatography / mass spectrometry
MeOH	Methanol
Min	Minutes
NBS	<i>N</i> -bromo succinimide
NCS	<i>N</i> -chloro succinimide
NIS	<i>N</i> -iodo succinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Prep.	Preparative

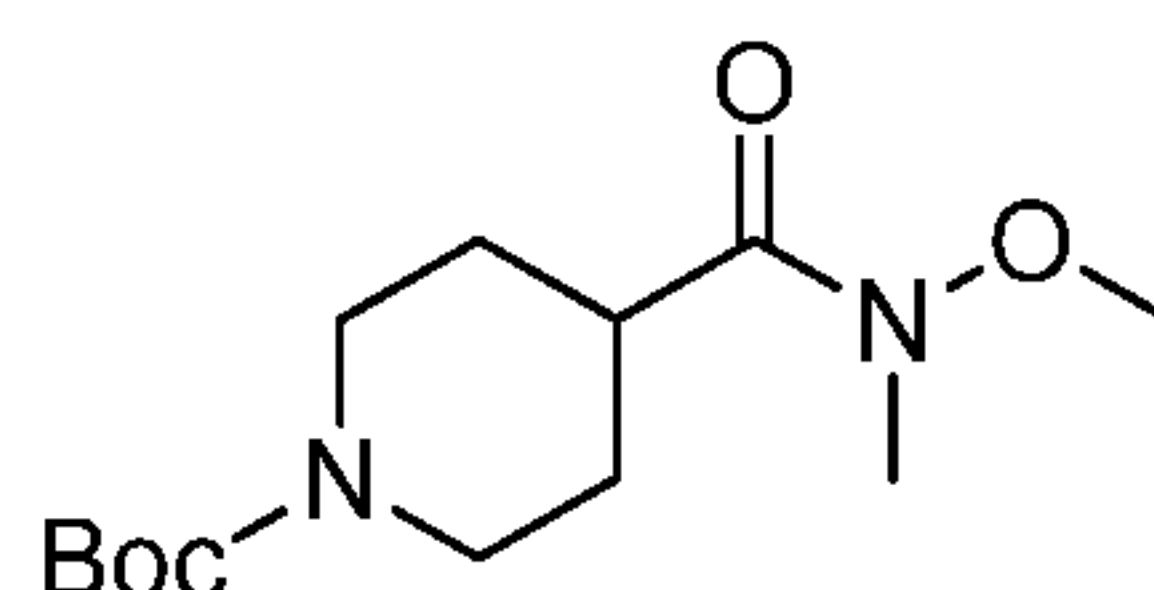
PTSA	<i>para</i> -toluene sulfonic acid
Rf	retardation factor
rt	room temperature
RT	retention time
sat.	Saturated
SGC	silica gel chromatography
TBAF	tetrabutyl ammonium fluoride
TEA	Triethylamine
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
TLC	thin layer chromatography
UPLC	ultra performance liquid chromatography

EXAMPLE 1

Synthesis of tert-butyl ((2S)-1-(4-(1-aminoethyl)piperidin-1-yl)-1-oxopropan-2-yl)carbamate

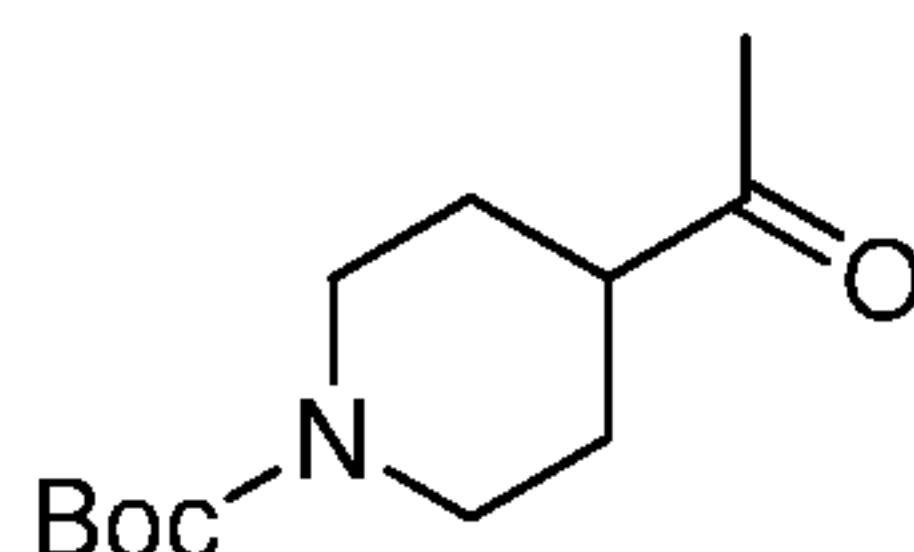


Step 1: Synthesis of tert-butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate



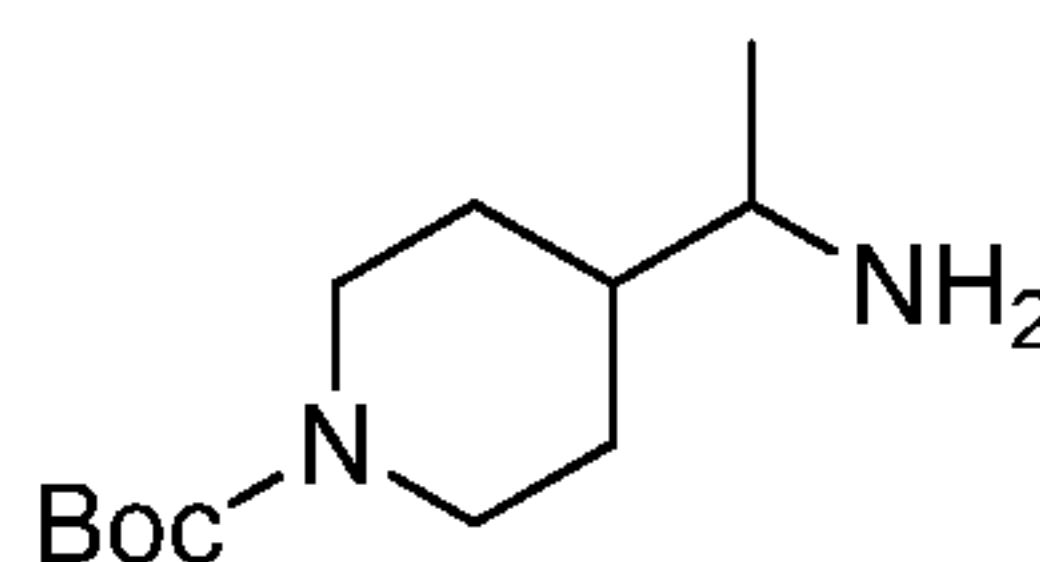
[0256] To a solution of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (20.0 g, 87.23 mmol) in DCM (200 mL) was added HATU (36.46 g, 95.95 mmol), TEA (17.62 g, 174.46 mmol) and N,O-dimethylhydroxylamine (8.93 g, 91.59 mmol). The mixture was stirred at 25 °C for 16 h. The mixture was washed with H₂O and the DCM layer was evaporated and the residue purified by silica column (PE/EA=1:1) to give the tert-butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (21.0 g, yield: 88.5%). ¹H NMR (400MHz, CDCl₃): δ = 4.27-4.01 (m, 2H), 3.71 (s, 3H), 3.19 (s, 3H), 2.85-2.70 (m, 3H), 1.75-1.62 (m, 4H), 1.46 (s, 9H).

Step 2: Synthesis of tert-butyl 4-acetylpiperidine-1-carboxylate



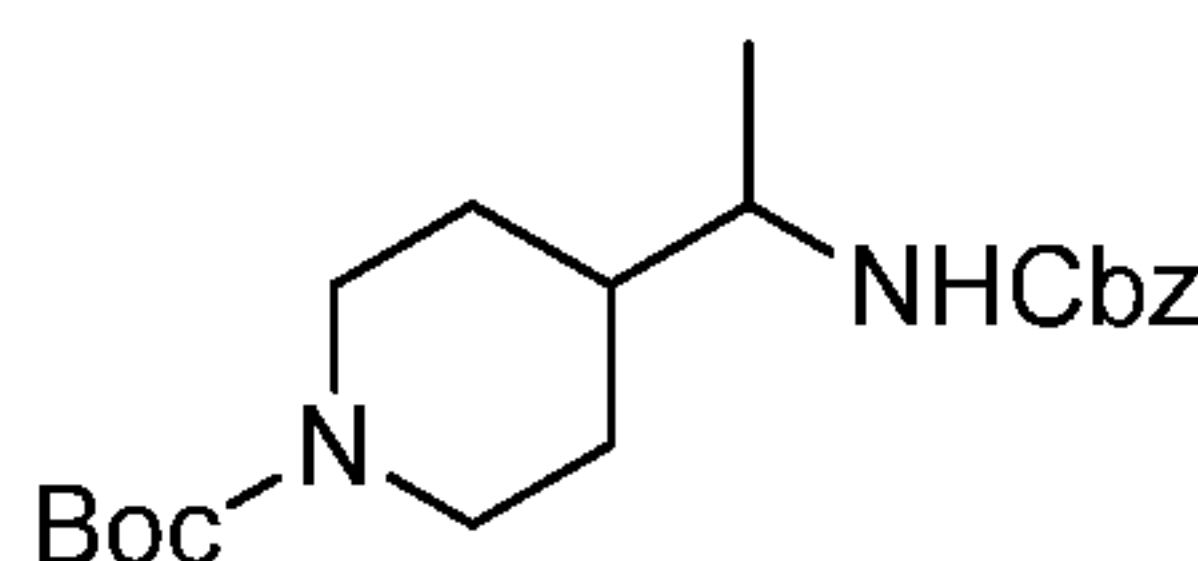
[0257] To a solution of tert-butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (10.0 g, 36.76 mmol) in THF (150 mL) was added MeMgBr (24.5 mL, 73.52 mmol) at -78 °C. The mixture was stirred at 25 °C for 16 h.. TLC showed the reaction worked well. The mixture was quenched with aq. NH₄Cl and H₂O (100 mL) was added. The mixture was extracted with DCM (100 mL x 3). The DCM layer was dried and evaporated to give the tert-butyl 4-acetylpiperidine-1-carboxylate (7.9 g, yield: 94.7 %). ¹H NMR (400MHz, CDCl₃): δ = 4.10 (br. s., 2H), 2.88-2.70 (m, 2H), 2.46 (tt, *J* = 3.6, 11.5 Hz, 1H), 2.17 (s, 3H), 1.84 (d, *J*=11.5 Hz, 2H), 1.58-1.48 (m, 2H), 1.48-1.41 (m, 9H).

Step 3: Synthesis of tert-butyl 4-(1-aminoethyl)piperidine-1-carboxylate



[0258] To a solution of tert-butyl 4-acetylpiperidine-1-carboxylate (7.9 g, 34.8 mmol) in MeOH (100 mL) was added NH₄OAc (10.72 g, 139.2 mmol) and AcOH (1 mL). The mixture was stirred at 25 °C for 2 h, then was added NaBH₃CN (2.63 g, 41.76 mmol). The mixture was stirred at 25 °C for 16 h. The mixture was evaporated and 2N NaOH (50 mL) was added to the residue. The solution was extracted with DCM (100 mL x 3). The DCM layer was washed with H₂O and brine dried and evaporated to give the tert-butyl 4-(1-aminoethyl)piperidine-1-carboxylate (7.93 g, yield: 100 %). ¹H NMR (400MHz, CDCl₃): δ = 4.15 (br. s., 2H), 2.77-2.57 (m, 3H), 1.76-1.59 (m, 2H), 1.46 (s, 9H), 1.33-1.10 (m, 5H), 1.06 (d, *J* = 6.5 Hz, 3H).

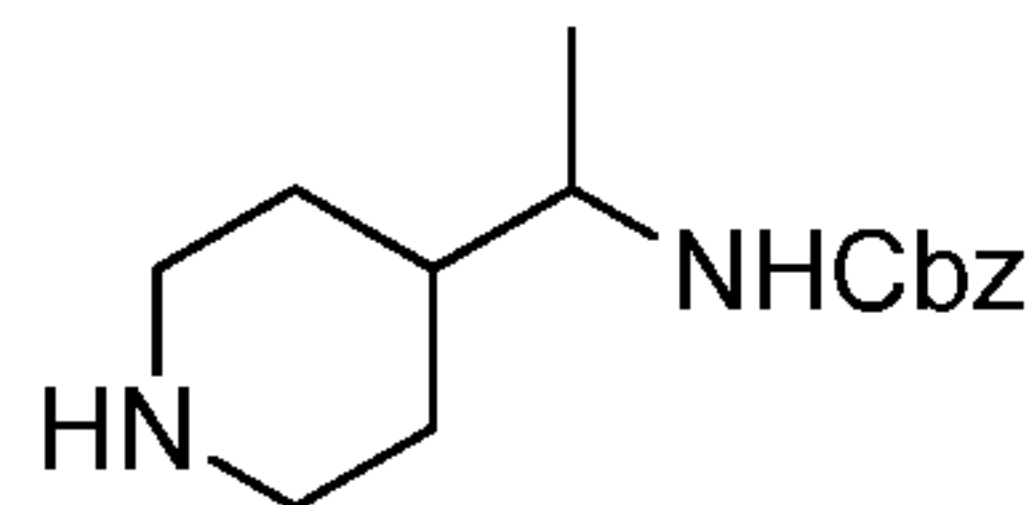
Step 4: Synthesis of tert-butyl 4-(1-(((benzyloxy)carbonyl)amino)ethyl)piperidine-1-carboxylate



[0259] To a solution of tert-butyl 4-(1-aminoethyl)piperidine-1-carboxylate (7.93 g, 34.8 mmol) in THF (80 mL) was added K₂CO₃ (9.6 g, 69.6 mmol) and Cbz-Cl (7.1 g, 41.76 mmol). The mixture was stirred at 25 °C for 16 h. The mixture diluted with H₂O and

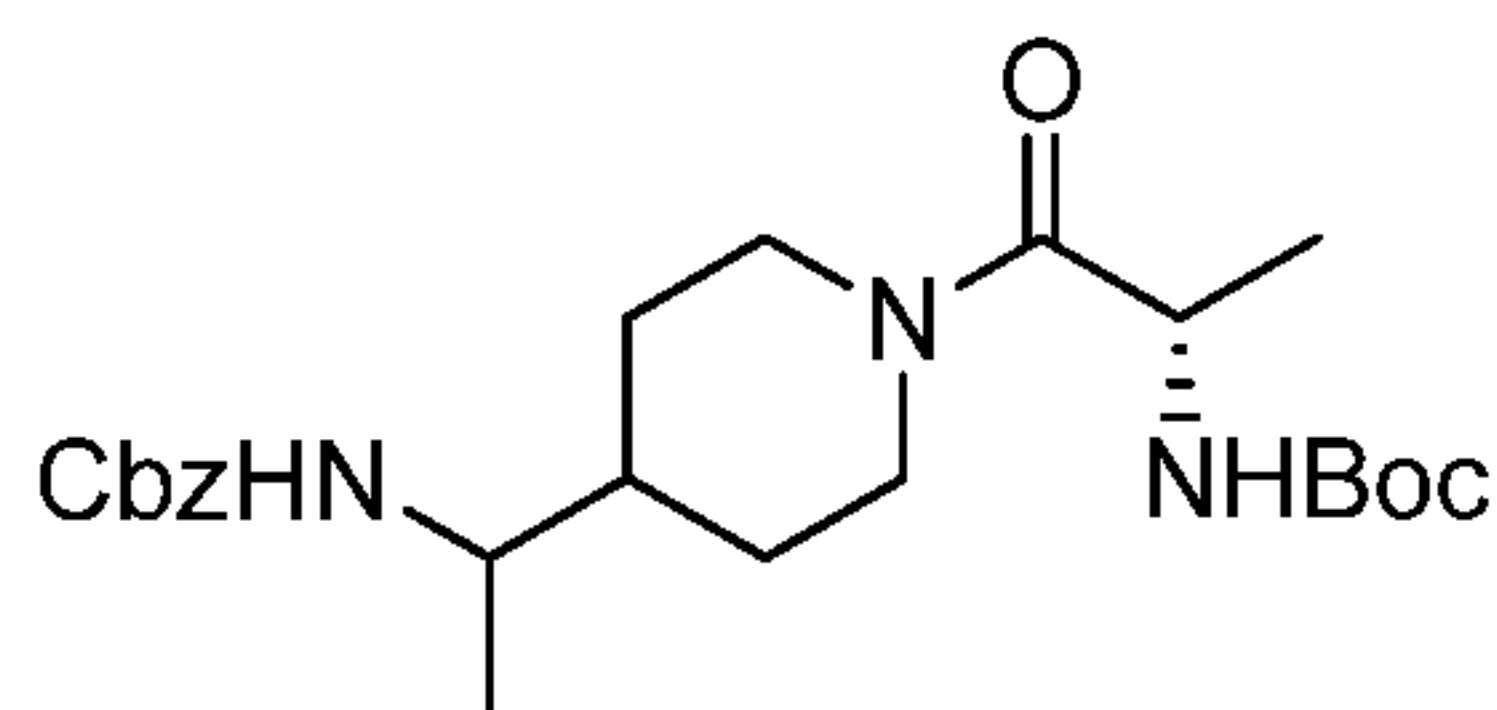
extracted with EA (50 mL x 3) and the EA layer evaporated to give tert-butyl 4-(1-(((benzyloxy)carbonyl)amino)ethyl)piperidine-1-carboxylate (10.1 g, yield: 80.2%). ¹H NMR (400MHz, DMSO-d₆): δ = 7.42-7.23 (m, 5H), 7.16 (d, *J*=8.8 Hz, 1H), 5.00 (s, 2H), 3.94 (d, *J*=11.8 Hz, 2H), 3.45-3.34 (m, 1H), 2.71-2.55 (m, 2H), 1.67-1.42 (m, 3H), 1.38 (s, 9H), 1.13-0.89 (m, 5H).

Step 5: Synthesis of benzyl (1-(piperidin-4-yl)ethyl)carbamate



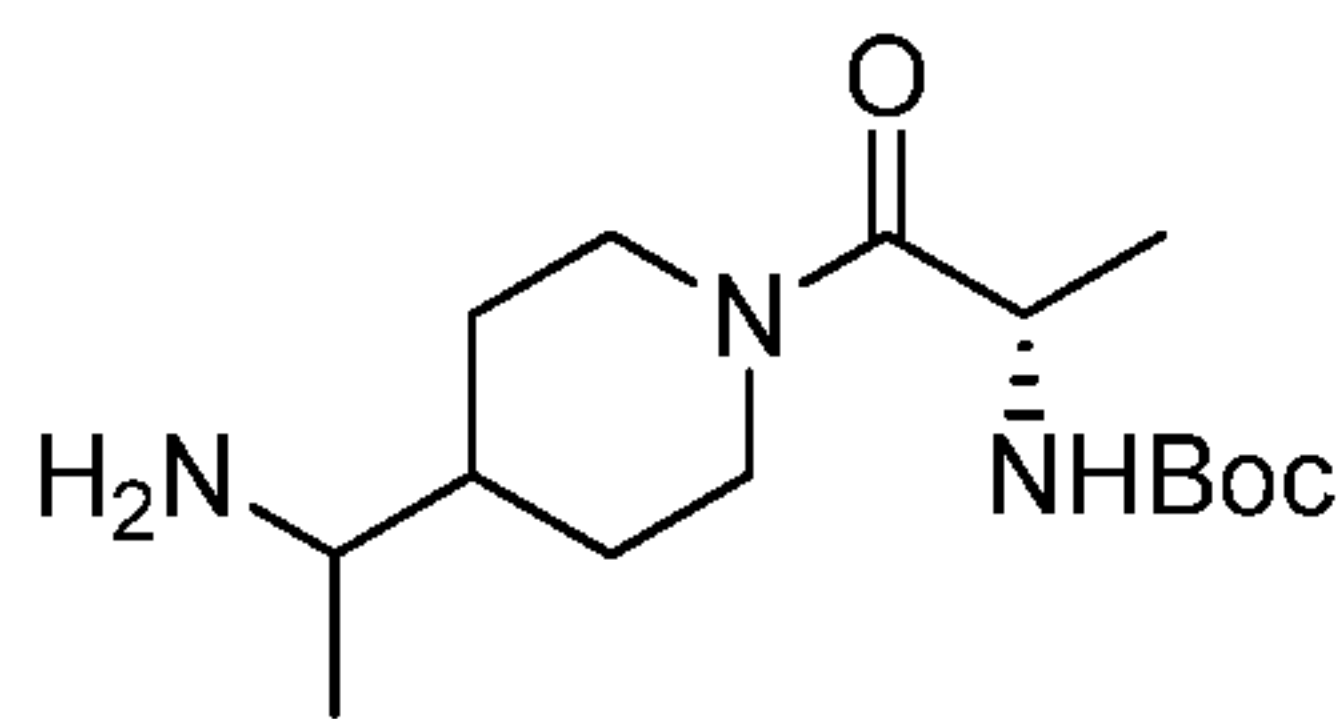
[0260] To a solution of tert-butyl 4-(1-(((benzyloxy)carbonyl)amino)ethyl)piperidine-1-carboxylate (10.1 g, 27.87 mmol) in EA (50 mL) was added HCl/EA (50 mL). The mixture was stirred at 25 °C for 16 h. Solvents were then evaporated to give the benzyl (1-(piperidin-4-yl)ethyl)carbamate as a white solid. (8.3 g, yield: 100%). ¹H NMR (400MHz, DMSO-d₆): δ = 8.88 (br. s., 1H), 8.50 (d, *J* = 9.5 Hz, 1H), 7.42-7.30 (m, 5H), 7.26 (d, *J* = 8.8 Hz, 1H), 5.04-4.98 (m, 2H), 3.46-3.41 (m, 1H), 3.24 (d, *J* = 11.8 Hz, 2H), 2.84-2.71 (m, 2H), 1.74 (d, *J*=13.6 Hz, 2H), 1.53 (d, *J*=3.8 Hz, 1H), 1.40-1.28 (m, 2H), 1.05-0.99 (m, 3H).

Step 6: Synthesis of tert-butyl N-[(1S)-2-[4-[1-(benzyloxycarbonylamino)ethyl]-1-piperidyl]-1-methyl-2-oxo-ethyl]carbamate



[0261] To a solution of benzyl (1-(piperidin-4-yl)ethyl)carbamate (7.0 g, 23.43 mmol) in DCM (100 mL) was added HATU (8.9 g, 23.43 mmol), TEA (4.73 g, 46.86 mmol) and (S)-2-((tert-butoxycarbonyl)amino)propanoic acid (4.43 g, 23.43 mmol). The mixture was stirred at 25 °C for 5 h. The mixture was washed with H₂O and the DCM layer evaporated. The residue was purified by silica column (PE/EA=1:1) to give the tert-butyl N-[(1S)-2-[4-[1-(benzyloxycarbonylamino)ethyl]-1-piperidyl]-1-methyl-2-oxo-ethyl]carbamate (8.9 g, yield: 87.7%). ¹H NMR (400MHz, CDCl₃): δ = 7.37 (s, 5H), 5.58 (br. s., 1H), 5.15-5.03 (m, 2H), 4.60 (dd, *J* = 7.4, 14.7 Hz, 3H), 3.96-3.86 (m, 1H), 3.68 (br. s., 1H), 2.99 (br. s., 1H), 2.54 (d, *J* = 11.0 Hz, 1H), 1.91-1.63 (m, 3H), 1.44 (br. s., 9H), 1.28 (d, *J* = 6.8 Hz, 4H), 1.21-1.07 (m, 4H).

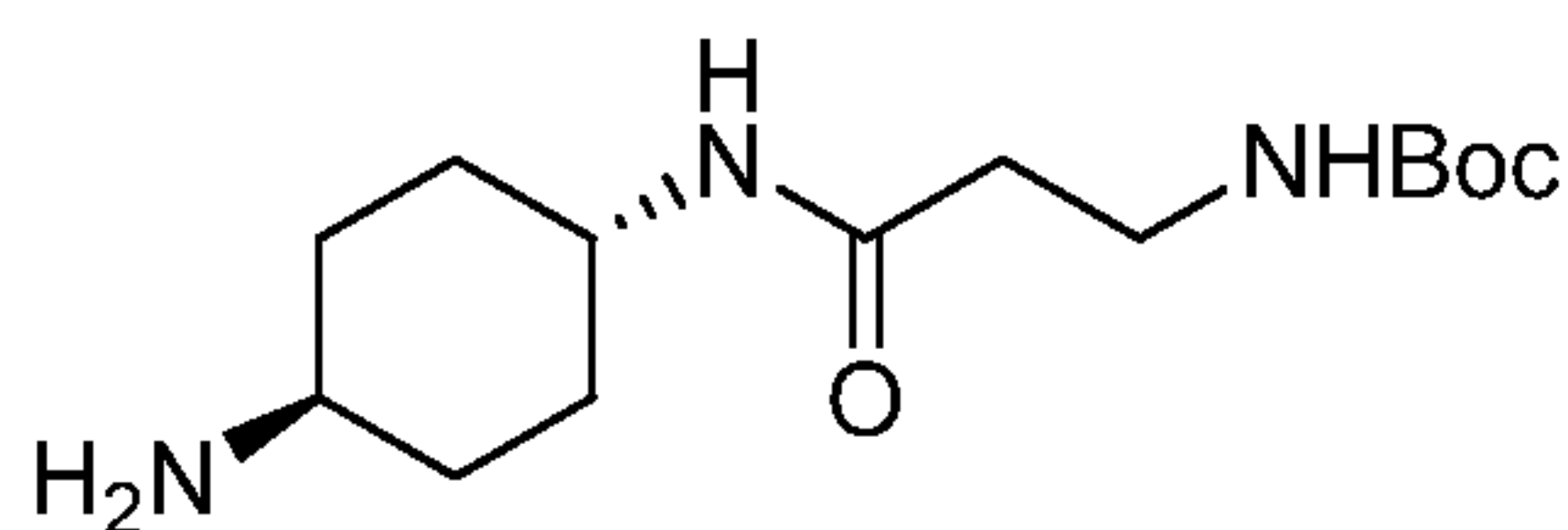
Step 7: Synthesis of tert-butyl ((2S)-1-(4-(1-aminoethyl)piperidin-1-yl)-1-oxopropan-2-yl)carbamate



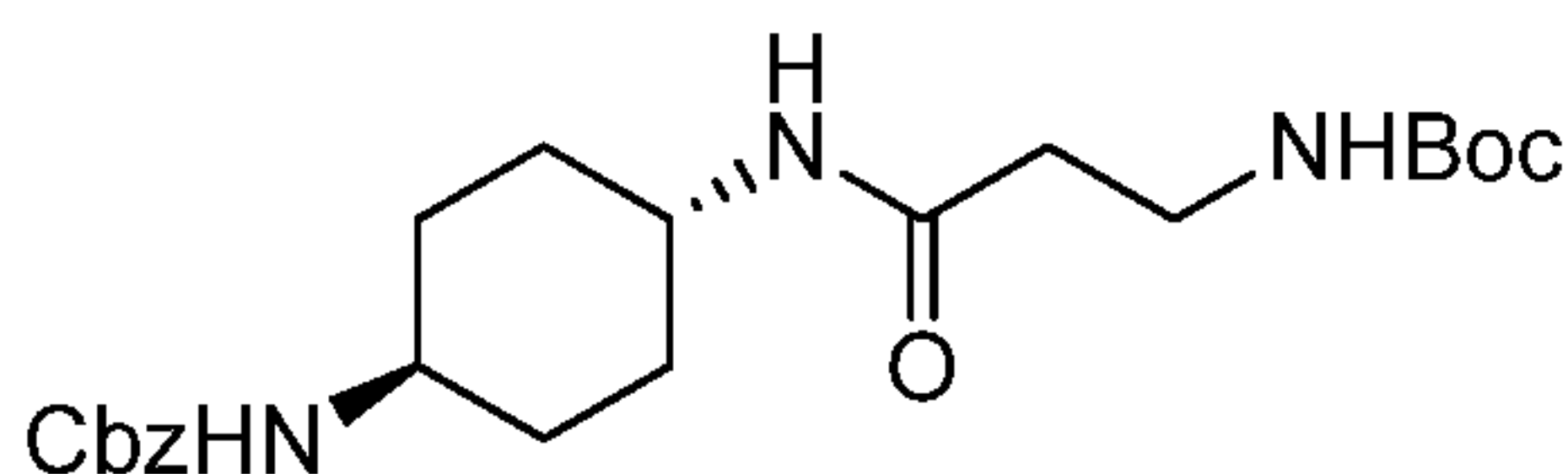
[0262] To a solution of tert-butyl N-[(1S)-2-[4-[1-(benzyloxycarbonylamino)ethyl]-1-piperidyl]-1-methyl-2-oxo-ethyl]carbamate (8.9 g, 20.55 mmol) in MeOH (100 mL) was added Pd/C (900 mg). The mixture was stirred at 25 °C for 16 hours under H₂ (50 psi). The reaction mixture was filtered and the filtrate was evaporated to give the tert-butyl ((2S)-1-(4-(1-aminoethyl)piperidin-1-yl)-1-oxopropan-2-yl)carbamate. (5.6 g, yield: 91.2%). ¹H NMR (400MHz, MeOD-d₄): δ = 5.61 (t, *J* = 7.2 Hz, 1H), 4.71-4.56 (m, 2H), 3.91 (br. s., 1H), 3.06-2.96 (m, 1H), 2.77-2.71 (m, 1H), 2.59-2.50 (m, 1H), 1.85-1.68 (m, 2H), 1.44 (d, *J* = 3.0 Hz, 9H), 1.35-1.22 (m, 4H), 1.19-1.04 (m, 4H); LCMS (*m/z*): 300.2 [M+H]⁺.

EXAMPLE 2

Synthesis of tert-butyl (3-(((1r,4r)-4-aminocyclohexyl)amino)-3-oxopropyl)carbamate



Step 1: Synthesis of tert-butyl N-[3-[[4-(benzyloxycarbonylamino)cyclohexyl]amino]-3-oxo-propyl]carbamate



[0263] To a solution of 3-((tert-butoxycarbonyl)amino)propanoic acid (8.38 g, 44.30 mmol, 1.10 Eq) and TEA (8.2 g, 80 mmol, 2.0 Eq) in DCM (500 mL) was added HATU (15.31 g, 40.27 mmol, 1.00 Eq) in one portion at 20 °C. The mixture was stirred at 20 °C for 30 minutes. Then benzyl N-(4-aminocyclohexyl)carbamate (10.00 g, 40.27 mmol, 1.00 Eq) was added in one portion at 20 °C. The mixture was stirred at 20 °C for 12 hr at which point LCMS analysis showed the reaction was complete. The mixture was washed with water (400 mL x 3) and extracted with DCM (600mL x 3). The combined organic

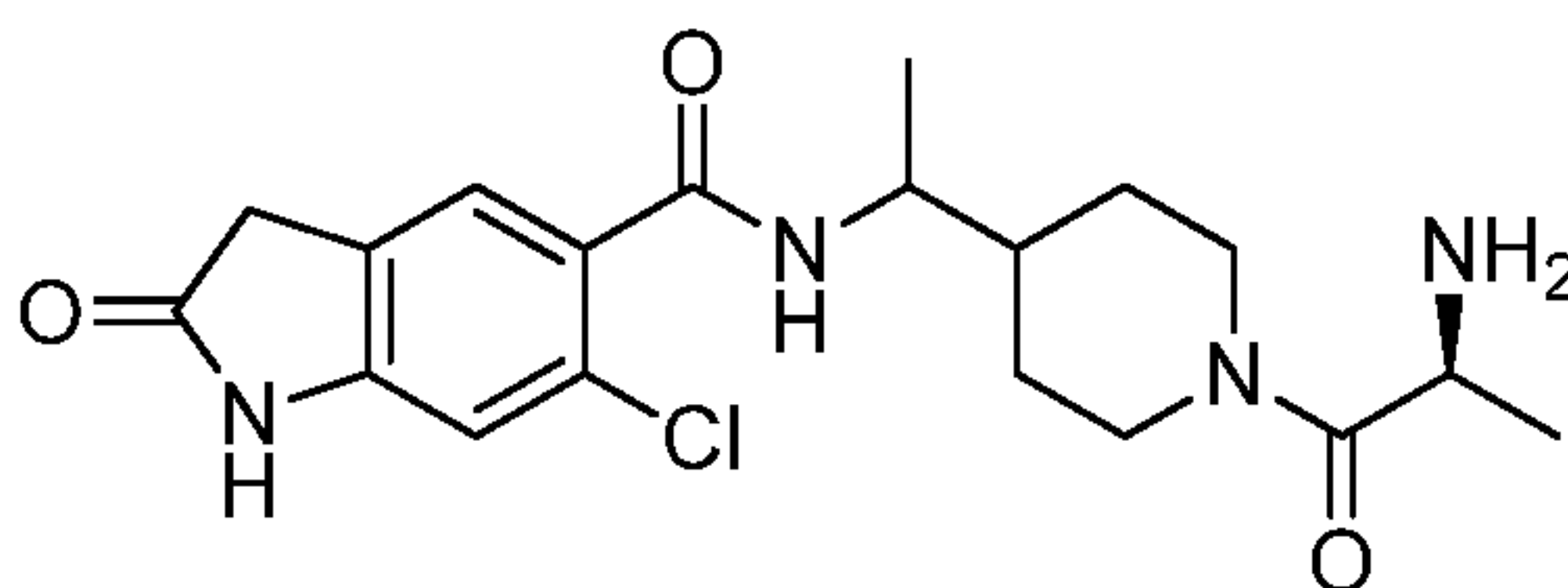
layer was concentrated in vacuum. The residue was purified by recrystallization (from minimum MeOH) to afford tert-butyl N-[3-[[4-(benzyloxycarbonylamino) cyclohexyl] amino]-3-oxo-propyl] carbamate (14.60 g, 34.80 mmol, 86.42% yield) as white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.74 (d, *J* = 7.78 Hz, 1 H), 7.31-7.40 (m, 5 H), 7.20 (d, *J* = 7.78 Hz, 1 H), 6.73 (t, *J* = 5.40 Hz, 1 H), 5.00 (s, 2 H), 3.44 (d, *J* = 6.78 Hz, 1 H), 3.23 (dd, *J* = 7.40, 3.14 Hz, 1 H), 3.10 (q, *J* = 6.61 Hz, 2 H), 2.18 (t, *J* = 7.40 Hz, 2 H), 1.78 (br. s., 4 H), 1.37 (s, 9 H), 1.16-1.27 (m, 4 H); LCMS (*m/z*): 320.2 [M+H-100]⁺.

Step 2: Synthesis of tert-butyl (3-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-3-oxopropyl) carbamate

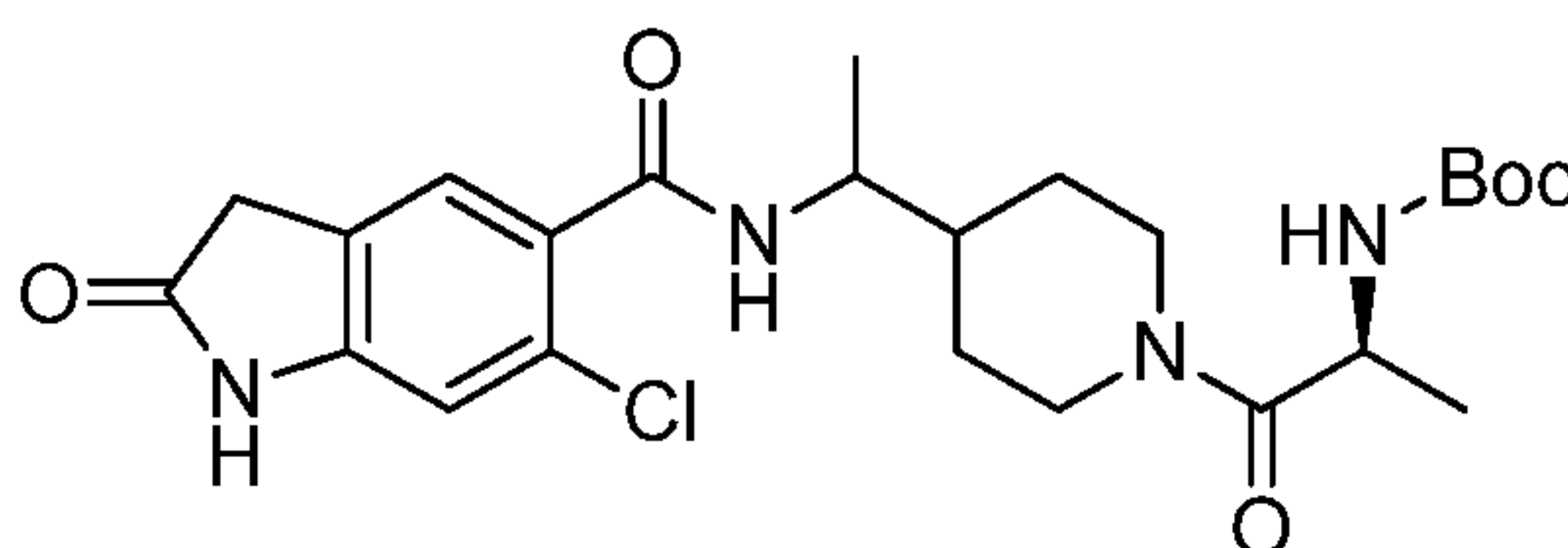
[0264] To a solution of tert-butyl N-[3-[[4-(benzyloxycarbonylamino) cyclohexyl]amino]-3-oxo-propyl]carbamate (14.60 g, 34.80 mmol, 1.00 Eq) in MeOH (500 mL) was added Pd/C (5 g) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50psi) at 50 °C for 12 hours. LCMS showed the starting material was consumed completely. The reaction mixture was filtered and concentrated to give tert-butyl N-[3-[(4-aminocyclohexyl) amino]-3-oxo-propyl]carbamate (9.80 g, 34.34 mmol, 98.67% yield) as yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.74 (d, *J* = 7.53 Hz, 1 H), 6.63-6.84 (m, 1 H), 3.43 (br. s., 1 H), 3.09 (q, *J* = 6.78 Hz, 2 H), 2.60 (br. s., 1 H), 2.18 (t, *J* = 7.28 Hz, 2 H), 1.70-1.82 (m, 4 H), 1.37 (s, 9 H), 1.08-1.20 (m, 4 H); LCMS (*m/z*): 230.2 [M+H-56]⁺.

EXAMPLE 3

Synthesis of N-(1-(1-((*S*)-2-aminopropanoyl)piperidin-4-yl)ethyl)-6-chloro-2-oxoindoline-5-carboxamide (Cpd. No. 490)

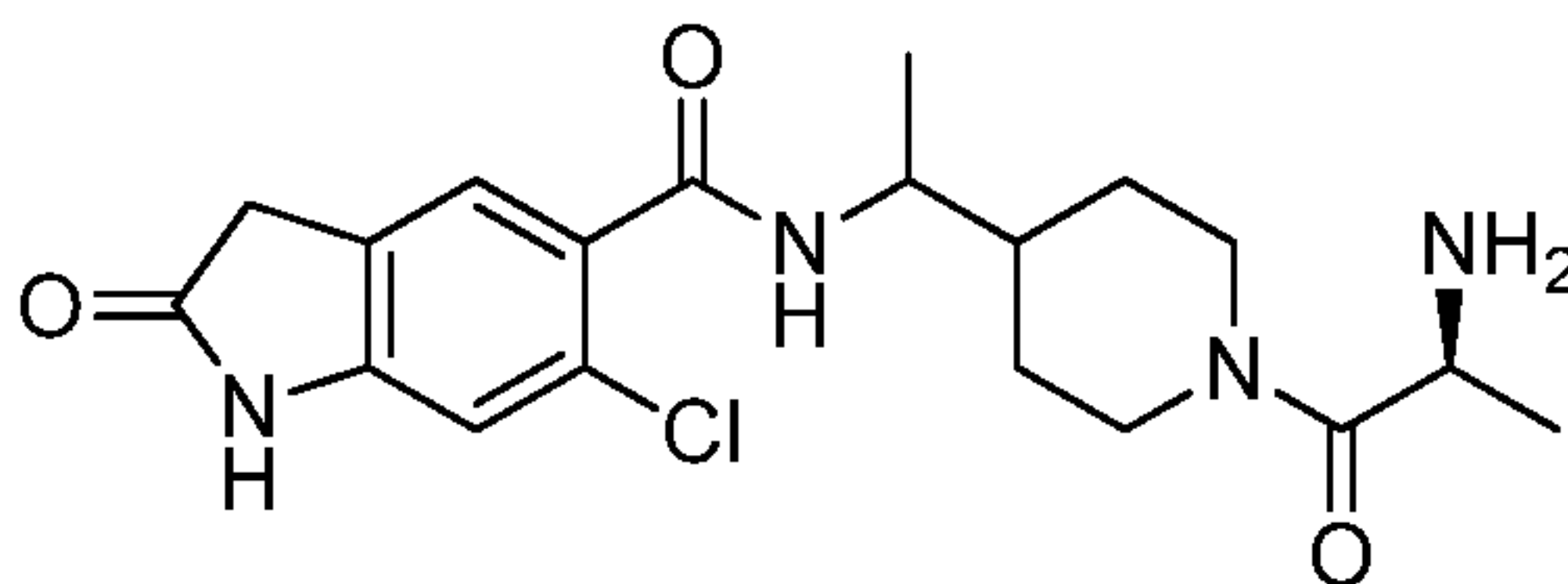


Step 1: Synthesis of ((2*S*)-1-(4-(1-(6-chloro-2-oxoindoline-5-carboxamido) ethyl)piperidin-1-yl)-1-oxopropan-2-yl)carbamate



[0265] To a mixture of 6-chloro-2-oxoindoline-5-carboxylic acid (100.00 mg, 472.59 μ mol, 1.00 Eq), HATU (179.69 mg, 472.59 μ mol, 1.00 Eq) and TEA (47.82 mg, 472.59 μ mol, 1.00 Eq) in DCM (10 mL) was added tert-butyl ((2S)-1-(4-(1-aminoethyl)piperidin-1-yl)-1-oxopropan-2-yl)carbamate (141.50 mg, 472.59 μ mol, 1.00 Eq). The mixture was stirred at 20 °C for 3 hours. LCMS showed the reaction was complete. Water (5 mL) was added to the reaction and the aqueous phase was extracted with DCM (10 mL x 3). The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford tert-butyl ((2S)-1-(4-(1-(6-chloro-2-oxoindoline-5-carboxamido)ethyl)piperidin-1-yl)-1-oxopropan-2-yl)carbamate (100.00 mg, crude). LCMS (m/z): 493.2 [M+H]⁺.

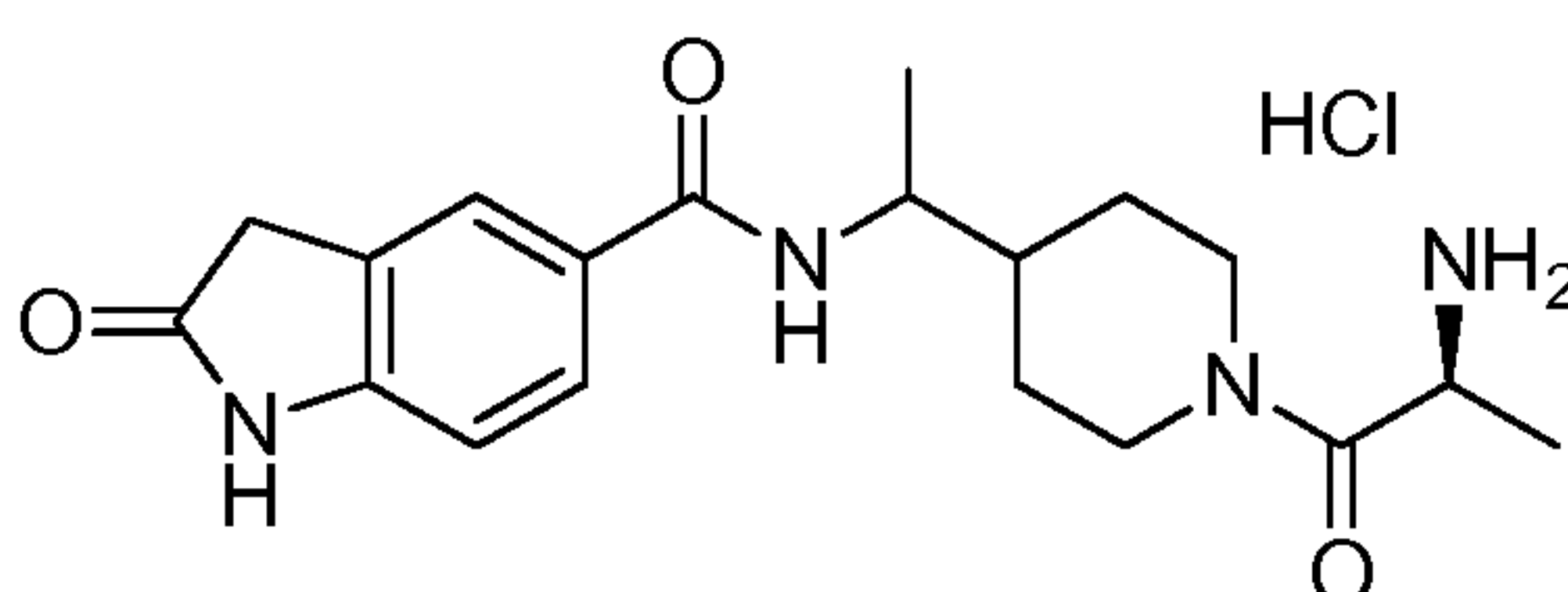
Step 2: Synthesis of N-(1-(1-((S)-2-aminopropanoyl)piperidin-4-yl)ethyl)-6-chloro-2-oxoindoline-5-carboxamide



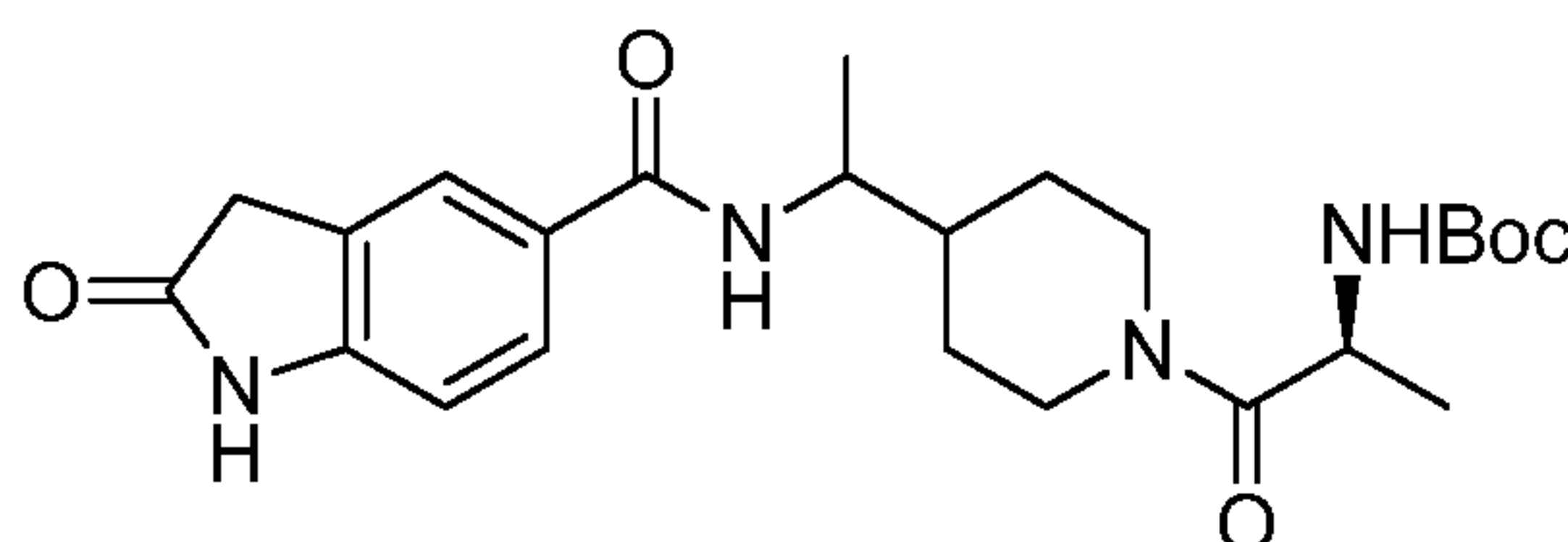
[0266] To a solution of tert-butyl ((2S)-1-(4-(1-(6-chloro-2-oxoindoline-5-carboxamido)ethyl)piperidin-1-yl)-1-oxopropan-2-yl)carbamate (100.00 mg, 202.84 μ mol, 1.00 Eq) in DCM (10 mL) was added dropwise TFA (3 mL) at 0 °C. The resulting solution was then stirred for 3 hours at 25 °C. TLC showed the reaction was complete. The mixture was evaporated and purified by prep-HPLC to afford N-(1-(1-((S)-2-aminopropanoyl)piperidin-4-yl)ethyl)-6-chloro-2-oxoindoline-5-carboxamide (38.50 mg, yield: 48.31%). ¹H NMR (400MHz, MeOD-d₄): δ = 7.29 (s, 1H), 6.95 (s, 1H), 4.56 (d, *J* = 12.5 Hz, 1H), 4.45-4.38 (m, 1H), 3.91 (d, *J* = 12.3 Hz, 2H), 3.54 (s, 2H), 3.15 (br. s., 2H), 2.72 - 2.63 (m, 1H), 2.01-1.85 (m, 2H), 1.75 (br. s., 1H), 1.46 (dd, *J* = 6.9, 11.7 Hz, 3H), 1.29-1.18 (m, 4H). LCMS (m/z): 393.2 [M+H]⁺.

EXAMPLE 4

Synthesis of N-(1-(1-((S)-2-aminopropanoyl)piperidin-4-yl)ethyl)-2-oxoindoline-5-carboxamide hydrochloride (Cpd. No. 86)

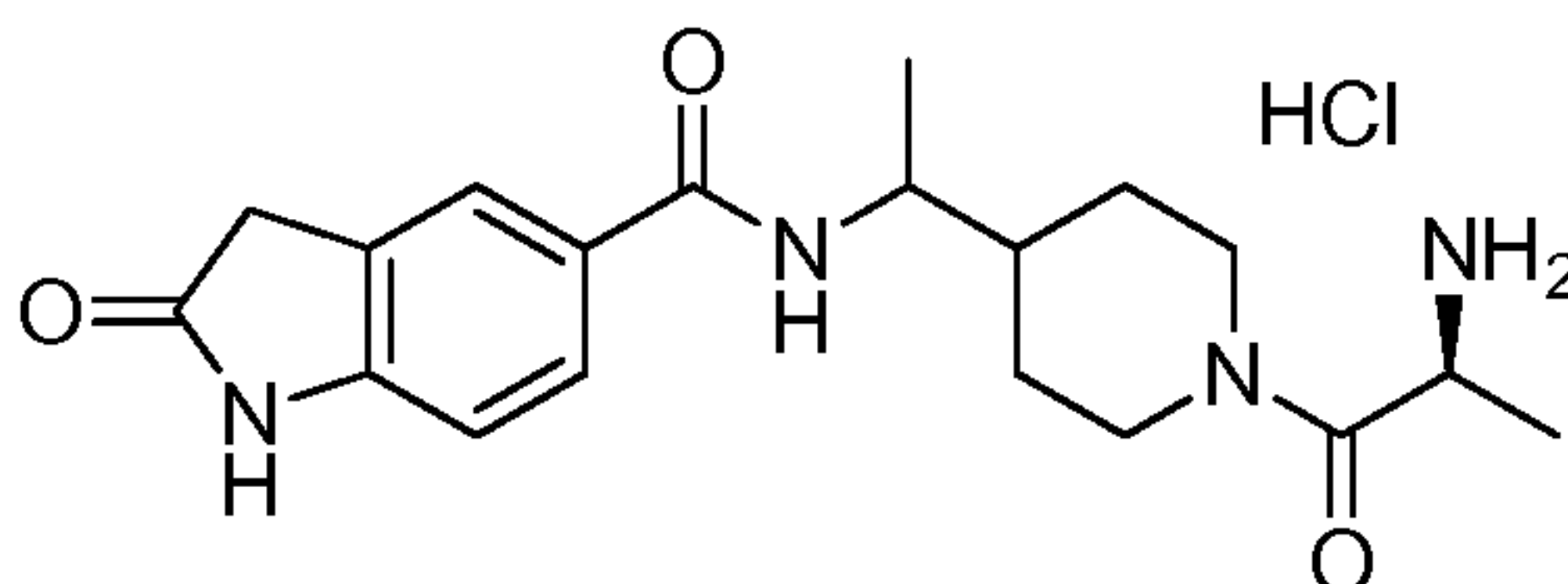


Step 1: Synthesis of tert-butyl ((2S)-1-oxo-1-(4-(1-(2-oxoindoline-5-carboxamido) ethyl) piperidin-1-yl) propan-2-yl) carbamate



[0267] To a stirred solution of 2-oxoindoline-5-carboxylic acid (0.177 g, 1.00 mmol) in DMF (2 mL), were added EDCI.HCl (0.24 g, 1.25 mmol), HOBt (0.168 g, 1.25 mmol) and triethylamine (0.35 mL, 2.5 mmol). The solution was stirred for 10 min at 0 °C. tert-Butyl ((2S)-1-(4-(1-aminoethyl)piperidin-1-yl)-1-oxopropan-2-yl)carbamate (0.25 g, 0.83 mmol) was added and the reaction stirred at rt for 6 h. The progress of the reaction was monitored by TLC. After complete consumption of starting material, the reaction was quenched with water and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain a crude residue which was purified by column chromatography to afford tert-butyl ((2S)-1-oxo-1-(4-(1-(2-oxoindoline-5-carboxamido)ethyl)piperidin-1-yl)propan-2-yl)carbamate (0.11 g, 28%). LCMS: 359.25 (M-Boc)⁺.

Step 2: Synthesis of N-(1-(1-((S)-2-aminopropanoyl)piperidin-4-yl)ethyl)-2-oxoindoline-5-carboxamide hydrochloride

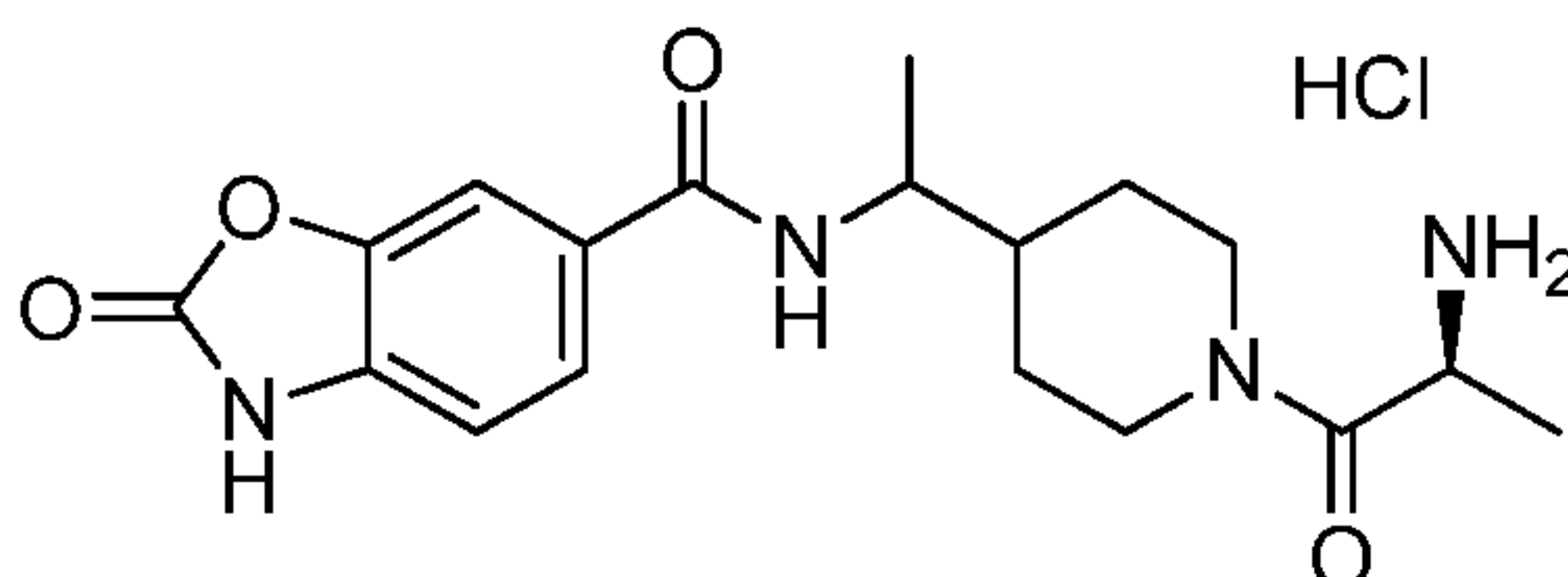


[0268] To a stirred solution of tert-butyl ((2S)-1-oxo-1-(4-(1-(2-oxoindoline-5-carboxamido)ethyl)piperidin-1-yl)propan-2-yl)carbamate (0.1 g, 0.47 mmol) in dioxane (2 mL) was added 4 M dioxane:HCl solution (4 mL) at 0 °C and the reaction mixture stirred at rt for 5 h. The progress of the reaction was monitored by TLC. After complete consumption of tert-butyl ((2S)-1-oxo-1-(4-(1-(2-oxoindoline-5-carboxamido)ethyl)piperidin-1-yl)propan-2-yl)carbamate, the solvent was removed under reduced pressure to obtain a crude residue which was purified by repeated washing with ether and pentane to obtain N-(1-(1-((S)-2-aminopropanoyl)piperidin-4-yl)ethyl)-2-oxoindoline-5-carboxamide hydrochloride (0.08 g, 93%). ¹H NMR (400 MHz, DMSO-d₆): δ 10.63 (s, 1H), 8.06 (q, *J* = 11.0, 8.4 Hz, 4H), 7.77-7.70 (m, 2H), 6.85 (d, *J* = 8.5 Hz, 1H), 4.38-4.35 (m, 2H), 3.85 (d, *J* = 13.9 Hz, 2H), 3.53 (s, 2H), 3.09-2.90 (m, 1H), 2.57 (dd, *J* =

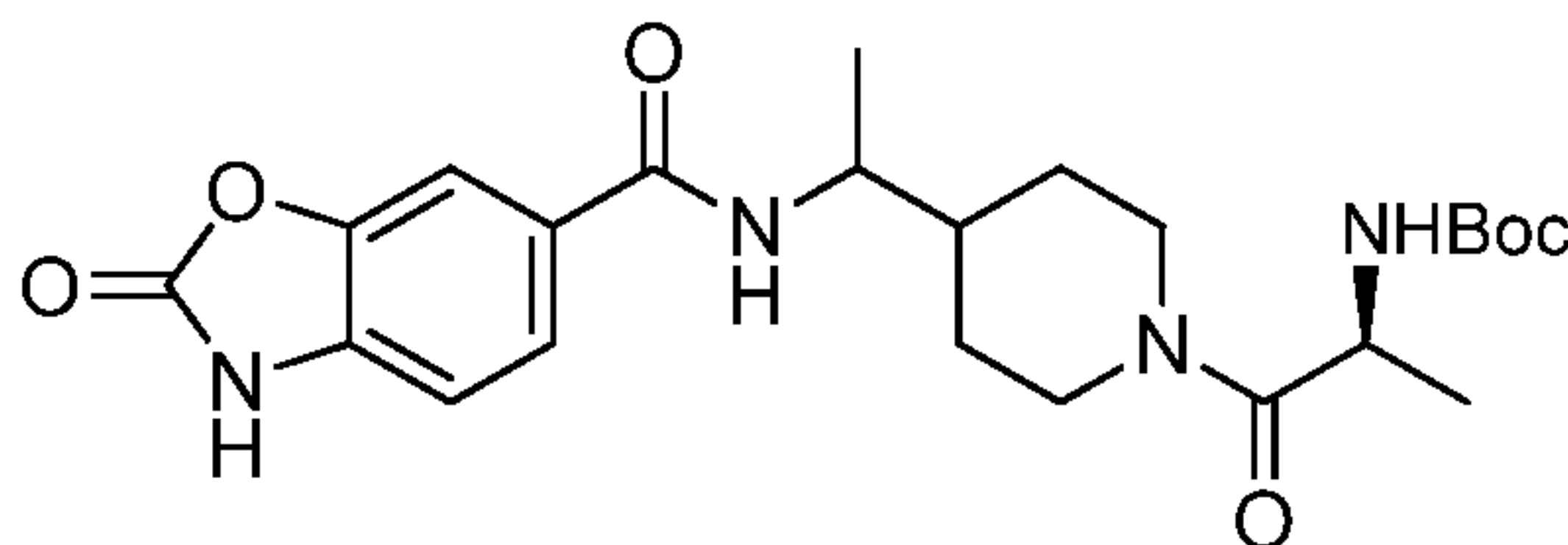
25.3, 12.8 Hz, 1H), 1.75 (dd, $J = 26.2, 12.6$ Hz, 3H), 1.3-1.28 (m, 3H), 1.12 (d, $J = 6.8$ Hz, 4H), 1.02 (d, $J = 12.5$ Hz, 1H); LCMS: 359.25 (M+1)⁺.

EXAMPLE 5

Synthesis of N-(1-(1-((S)-2-aminopropanoyl)piperidin-4-yl)ethyl)-2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxamide hydrochloride (Cpd. No. 94)

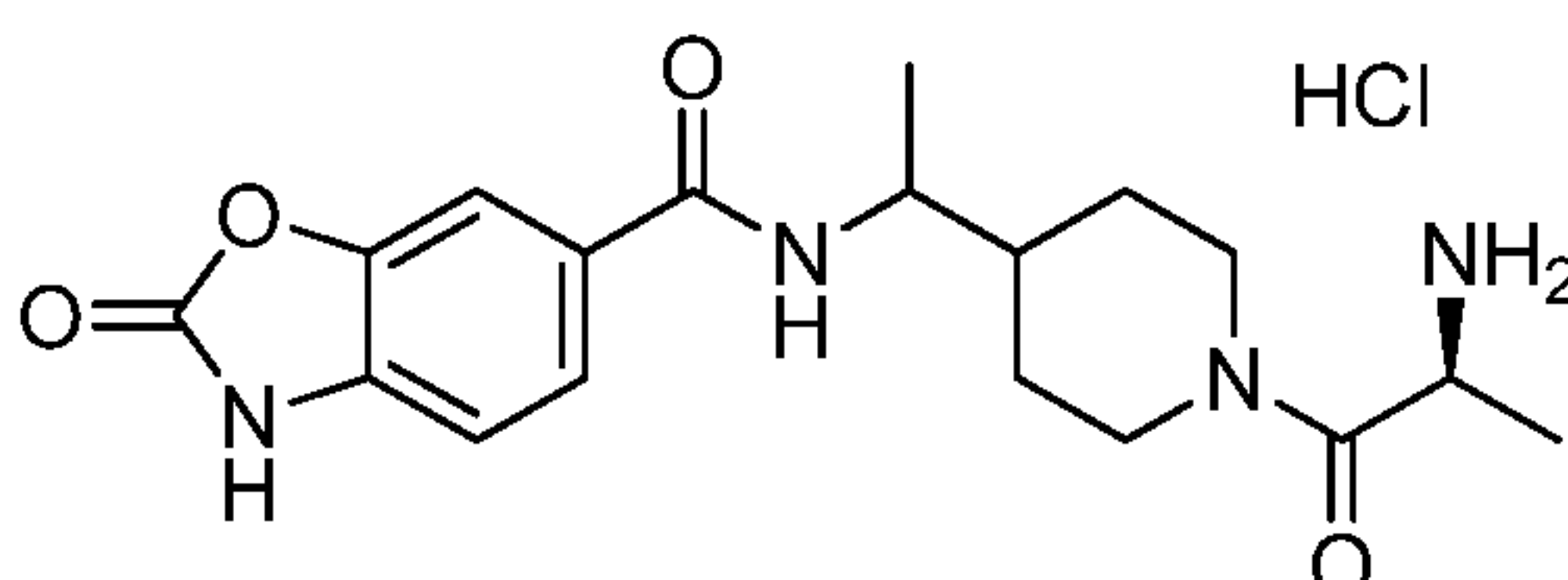


Step 1: Synthesis of tert-butyl ((2S)-1-oxo-1-(4-(1-(2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxamido)ethyl)piperidin-1-yl)propan-2-yl)carbamate



[0269] To a stirred solution of 2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxylic acid (0.2 g, 0.66 mmol) in DMF (1.5 mL) was added EDCI.HCl (0.191 g, 1.00 mmol), HOBt (0.091 g, 0.66 mmol) and diisopropylethylamine (0.34 mL, 2.00 mmol). The solution was stirred for 10 min at 0 °C. After that, tert-butyl ((2S)-1-(4-(1-aminoethyl)piperidin-1-yl)-1-oxopropan-2-yl)carbamate (0.142 g, 0.80 mmol) was added and the reaction stirred at rt for 12 h. The progress of the reaction was monitored by TLC. After complete consumption of starting material, the reaction was quenched with water and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain a crude residue which was purified by column chromatography to afford tert-butyl ((2S)-1-oxo-1-(4-(1-(2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxamido)ethyl)piperidin-1-yl)propan-2-yl)carbamate (0.104 g, 33%). LCMS: 361.05 (M-Boc)⁺.

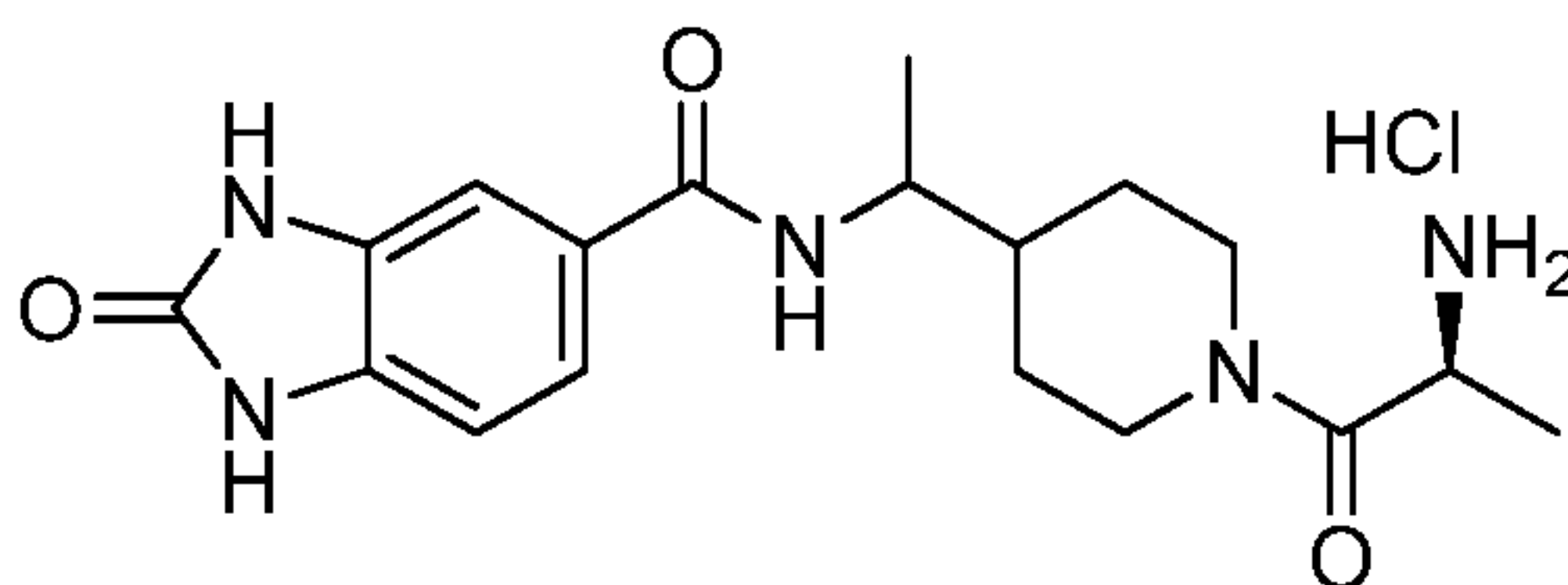
Step 2: Synthesis of N-(1-(1-((S)-2-aminopropanoyl)piperidin-4-yl)ethyl)-2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxamide hydrochloride



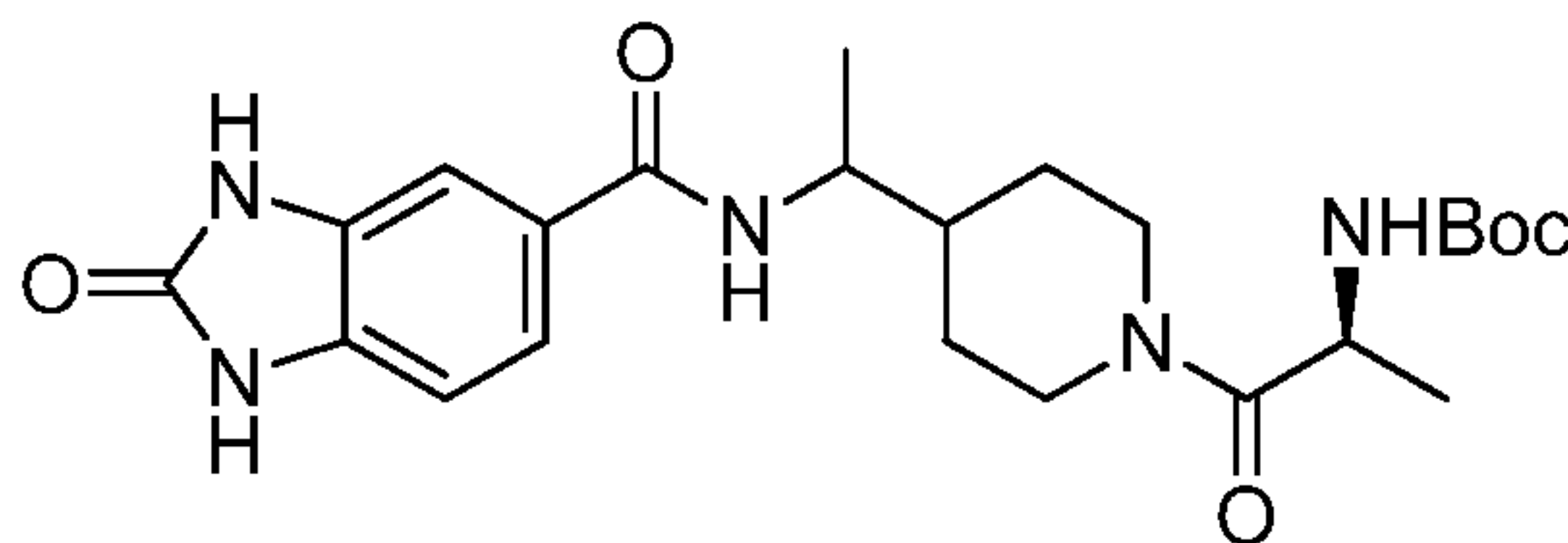
[0270] To a stirred solution of ((2S)-1-oxo-1-(4-(1-(2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxamido)ethyl)piperidin-1-yl)propan-2-yl)carbamate (0.03 g, 0.08 mmol) in dioxane (1 mL) at 0 °C was added 4M dioxane:HCl solution (1 mL). The reaction mixture was stirred at rt for 3 h. The progress of the reaction was monitored by TLC. After complete consumption of starting material, the solvent was removed under reduced pressure to obtain a crude residue which was purified by repeated washing with ether and hexane to obtain N-(1-(1-((S)-2-aminopropanoyl)piperidin-4-yl)ethyl)-2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxamide hydrochloride (0.008 g, 36%). ¹H NMR (400 MHz, DMSO-d₆): δ 10.66 (s, 1H), 8.72 (d, *J* = 12.3 Hz, 1H), 8.42 (q, *J* = 8.1, 7.1 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.1 Hz, 1H), 3.54 (s, 2H), 3.25 (d, *J* = 12.4 Hz, 2H), 3.16 (t, *J* = 6.1 Hz, 2H), 2.82 (q, *J* = 11.8 Hz, 2H), 2.62 (s, 1H), 1.79 (d, *J* = 13.4 Hz, 2H), 1.35-1.32 (m, 2H); LCMS: 274.15 (M+H)⁺

EXAMPLE 6

Synthesis of N-(1-(1-((S)-2-aminopropanoyl)piperidin-4-yl)ethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxamide (Cpd. No. 93)



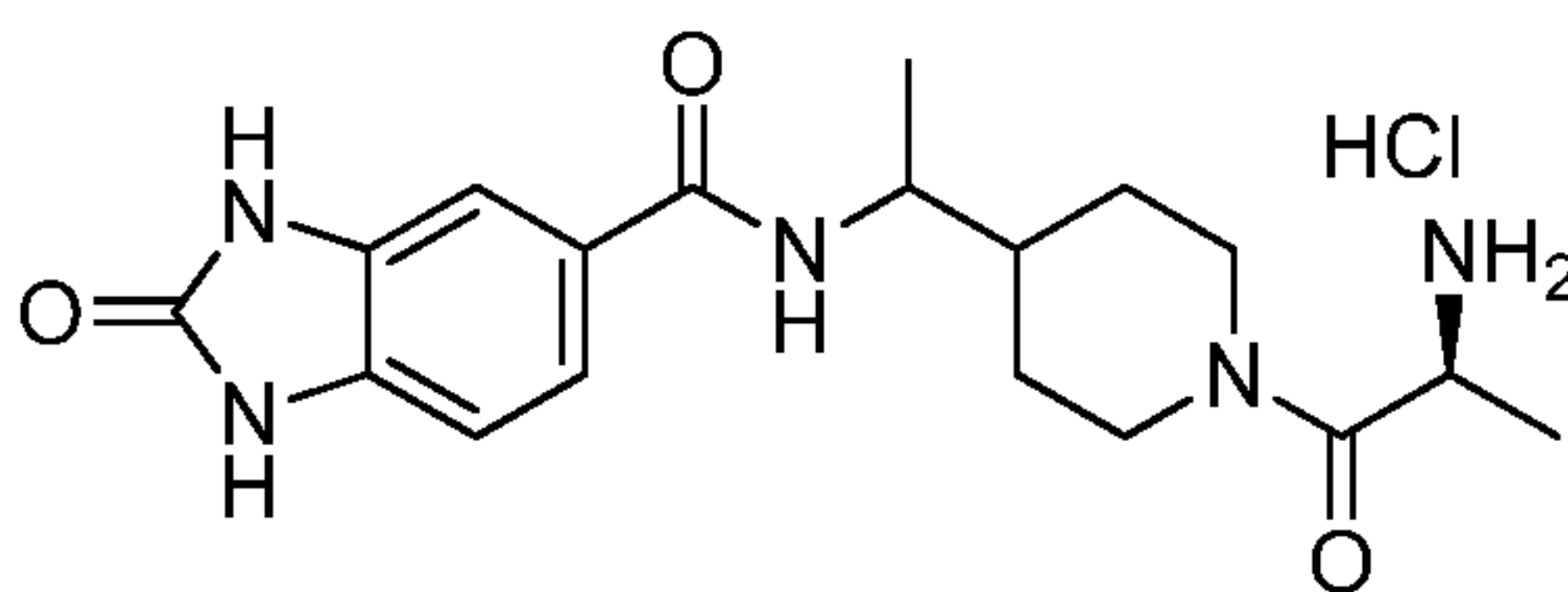
Step 1: Synthesis of N-(1-(1-((S)-2-aminopropanoyl)piperidin-4-yl)ethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxamide hydrochloride



[0271] To a stirred solution of 2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxylic acid (0.2 g, 0.66 mmol) in DMF (1.5 mL) was added EDCI.HCl (0.191 g, 1.00 mmol), HOBt (0.091g, 0.66 mmol) and diisopropylethylamine (0.34 mL, 2.00 mmol). The solution was stirred for 10 min at 0 °C. After that tert-butyl ((2S)-1-(4-(1-aminoethyl)piperidin-1-yl)-1-oxopropan-2-yl)carbamate (0.142 g, 0.80 mmol) was added and the reaction stirred at rt for 12 h. The progress of the reaction was monitored by TLC. After complete consumption of starting material, the reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over

anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a crude residue which was purified by column chromatography to afford tert-butyl ((2S)-1-oxo-1-(4-(1-(2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxamido)ethyl)piperidin-1-yl)propan-2-yl)carbamate (0.140 g, 45%). LCMS: 360.2 (M-Boc)⁺.

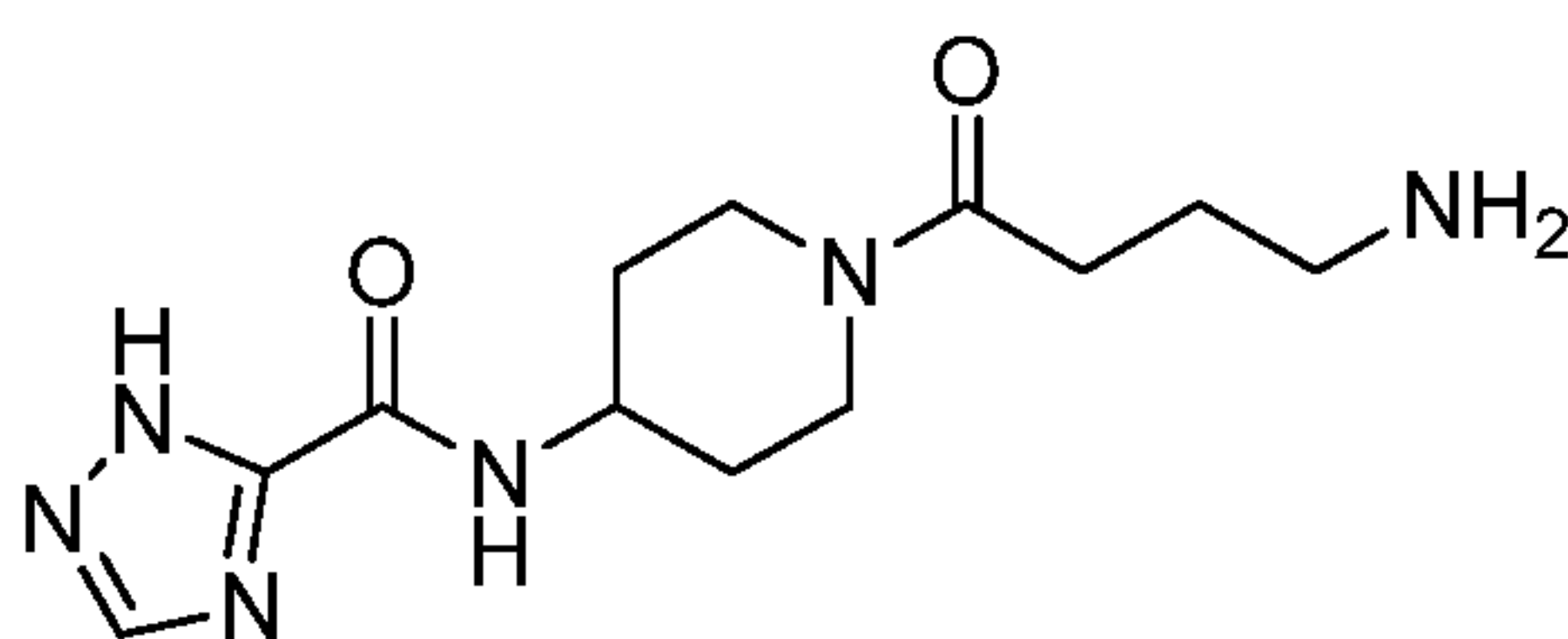
Step 2: Synthesis of N-(1-(1-((S)-2-aminopropanoyl)piperidin-4-yl)ethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxamide hydrochloride



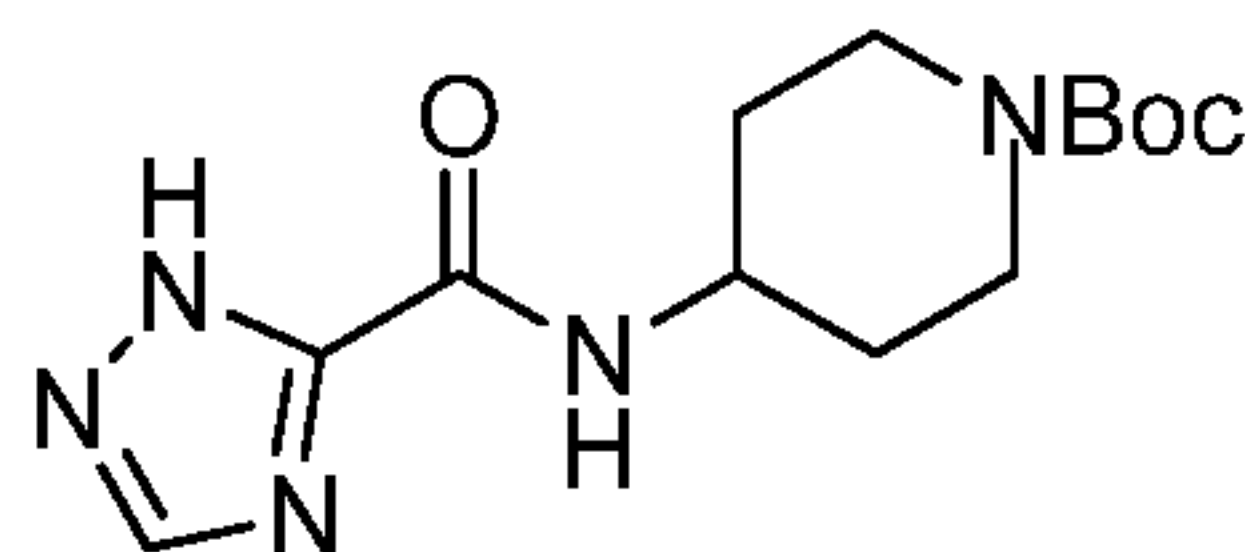
[0272] To a stirred solution of tert-butyl ((2S)-1-oxo-1-(4-(1-(2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxamido)ethyl)piperidin-1-yl)propan-2-yl)carbamate (0.1 g, 0.21 mmol) in dioxane (2 mL) at 0 °C was added 4M dioxane:HCl solution (1 mL). The reaction mixture was stirred at rt for 3 h. The progress of the reaction was monitored by TLC. After complete consumption of the starting material, the solvent was removed under reduced pressure to obtain a crude residue which was purified by repeated washing with ether and hexane to obtain N-(1-(1-((S)-2-aminopropanoyl)piperidin-4-yl)ethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxamide hydrochloride (0.060 g, 69%). ¹H NMR (400 MHz, DMSO- d_6): δ 10.85 (d, J = 16.4 Hz, 2H), 8.10 (p, J = 8.9, 7.6 Hz, 4H), 7.55-7.52 (m, 1H), 7.44 (q, J = 2.0 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 4.44-4.24 (m, 2H), 3.88-3.86 (m, 2H), 3.09-2.91 (m, 1H), 2.6-2.57 (m, 1H), 1.83-1.64 (m, 3H), 1.33-0.99 (m, 8H); LCMS: 360.25 (M+1)⁺.

EXAMPLE 7

N-(1-(4-aminobutanoyl)piperidin-4-yl)-1H-1,2,4-triazole-5-carboxamide (Cpd. No. 560)

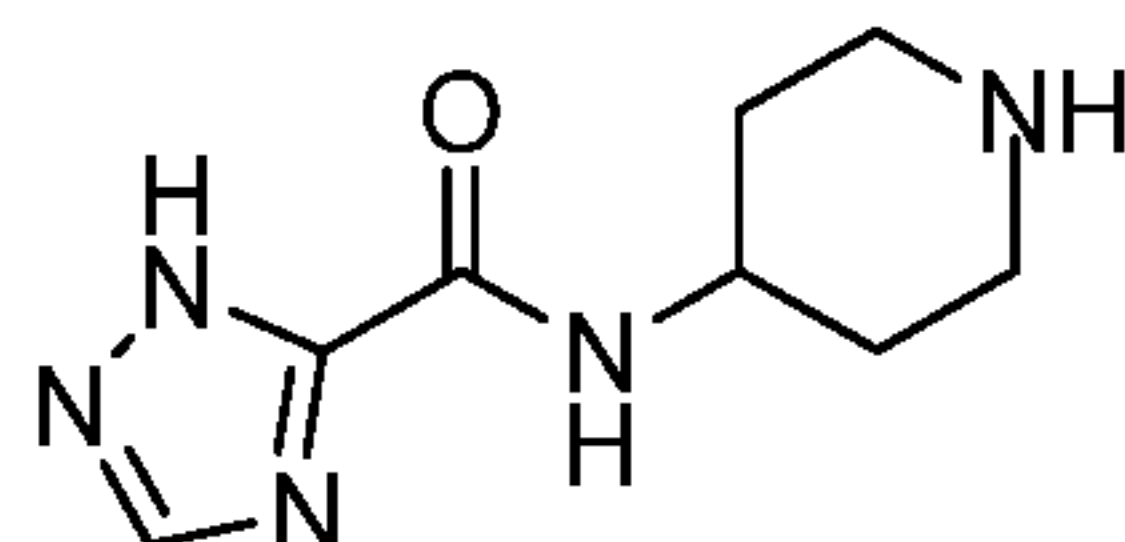


Step 1: Synthesis of tert-butyl 4-(1H-1,2,4-triazole-5-carboxylamino)piperidine-1-carboxylate



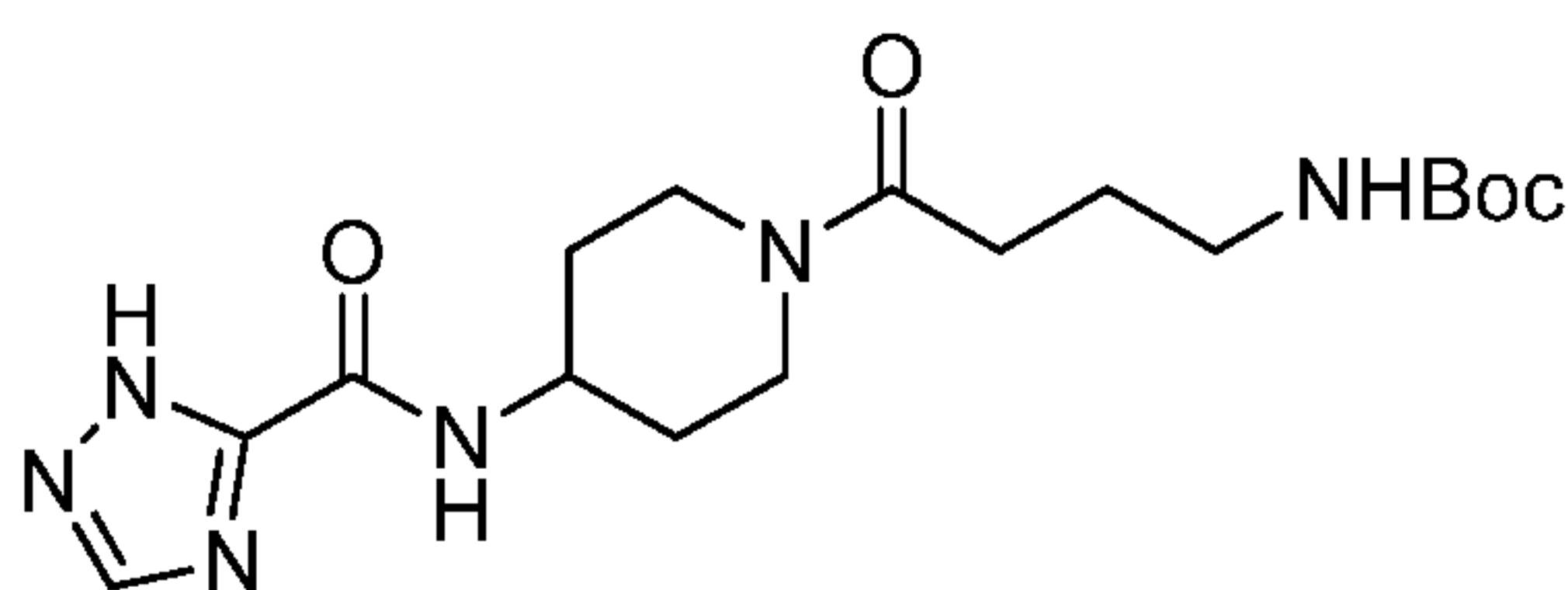
[0273] To a solution of 1H-1,2,4-triazole-5-carboxylic acid (2.00 g, 17.69 mmol, 1.00 Eq) in DMF (100 mL) was added TEA (2.68 g, 26.53 mmol, 1.50 Eq), BOP-Cl (4.95 g, 19.46 mmol, 1.10 Eq), and tert-butyl 4-aminopiperidine-1-carboxylate (3.90 g, 19.46 mmol, 1.10 Eq). The reaction mixture was stirred at 20 °C for 12 hr. The reaction mixture was concentrated and dissolved in MeOH, filtered, the organic layer was concentrated and purified by silica gel column chromatography to give tert-butyl 4-(1H-1,2,4-triazole-5-carboxamido)piperidine-1-carboxylate (3.13 g, 10.60 mmol, 59.9% yield) as a yellow solid. LCMS (m/z): 240.1 [M+H]⁺.

Step 2: Synthesis of N-(4-piperidyl)-1H-1,2,4-triazole-5-carboxamide



[0274] To a solution of tert-butyl 4-(1H-1,2,4-triazole-5-carboxamido)piperidine-1-carboxylate (3.13 g, 10.60 mmol, 1.00 Eq) in DCM (50 mL) was added TFA (10 mL). The reaction mixture was stirred at 20 °C for 5 hr. The reaction mixture was concentrated and lyophilized to afford N-(4-piperidyl)-1H-1,2,4-triazole-5-carboxamide (6.00 g, 19.40 mmol, 91.51% yield) as a light yellow solid. LCMS (m/z): 196.2 [M+H]⁺

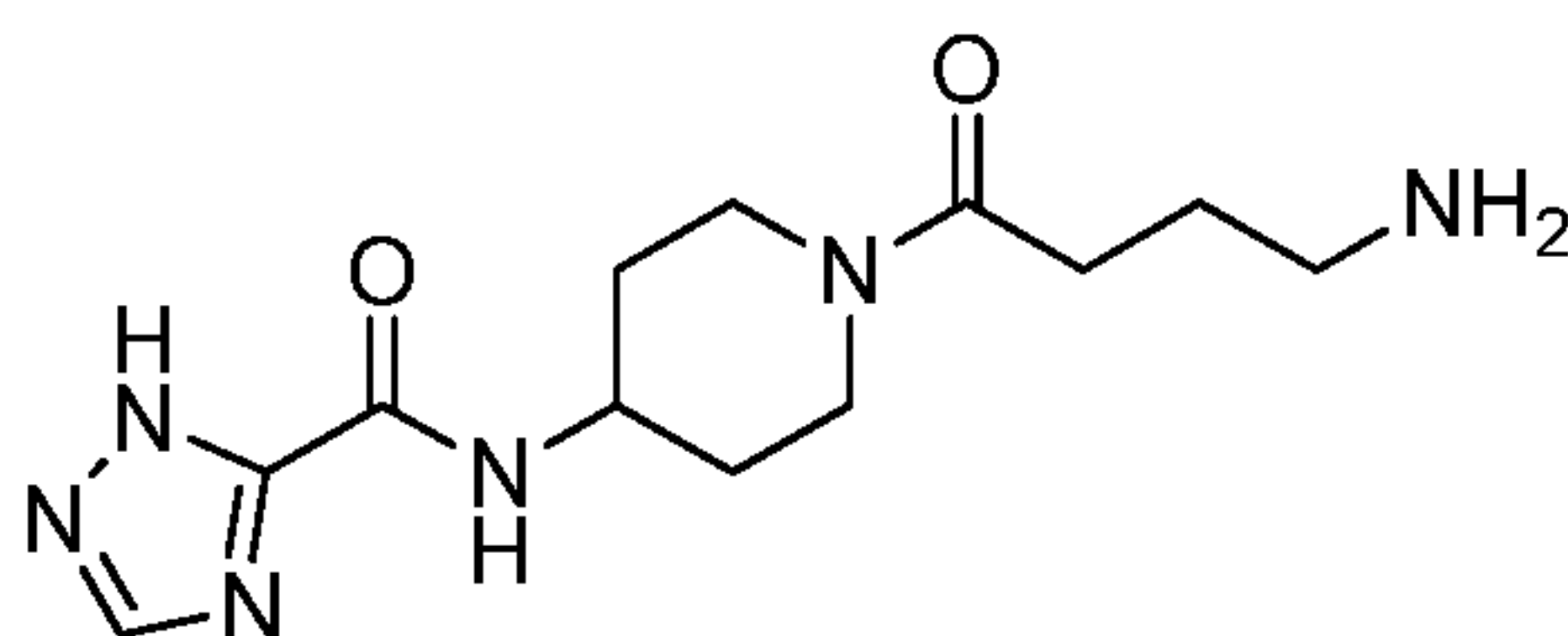
Step 3: Synthesis of tert-butyl (4-(4-(1H-1,2,4-triazole-5-carboxamido)piperidin-1-yl)-4-oxobutyl)carbamate



[0275] To a mixture of 4-((tert-butoxycarbonyl)amino)butanoic acid (203.00 mg, 998.87 umol, 1.00 q) and HATU (379.80 mg, 998.87 umol, 1.00 Eq) in DCM (10 mL) was added Et₃N (202.15 mg, 2.00 mmol, 2.00 Eq) in one portion at 20 °C. The mixture was stirred at 20 °C for 30 min. Then N-(piperidin-4-yl)-1H-1,2,4-triazole-5-carboxamide (195.00 mg, 998.87 umol, 1.00 Eq) was added in one portion at 20 °C. The mixture was stirred at 20 °C for 12 h. LCMS showed the reaction was complete. The reaction mixture was washed with water (40 mL x 3) and extracted with DCM (50 mL x 3). The combined organic layer was concentrated under vacuum. The residue was purified by prep-HPLC to

afford tert-butyl (4-(4-(1H-1,2,4-triazole-5-carboxamido)piperidin-1-yl)-4-oxobutyl)carbamate (200.00 mg, 525.71 μ mol, 52.63% yield) as white solid. ^1H NMR (400 MHz, MeOD-d_4) δ 8.45 (s, 1 H) 4.54 (d, $J = 13.30$ Hz, 1 H) 4.13-4.21 (m, 1 H) 4.01 (d, $J = 13.80$ Hz, 1 H) 3.23-3.30 (m, 1 H) 3.11 (t, $J = 6.78$ Hz, 2 H) 2.85 (t, $J = 11.67$ Hz, 1 H) 2.46 (t, $J = 7.53$ Hz, 2 H) 1.97-2.07 (m, 2 H) 1.78 (quin, $J = 7.15$ Hz, 2 H) 1.53-1.65 (m, 2 H) 1.38-1.53 (m, 9 H); LCMS (m/z): 381.2 $[\text{M}+\text{H}]^+$.

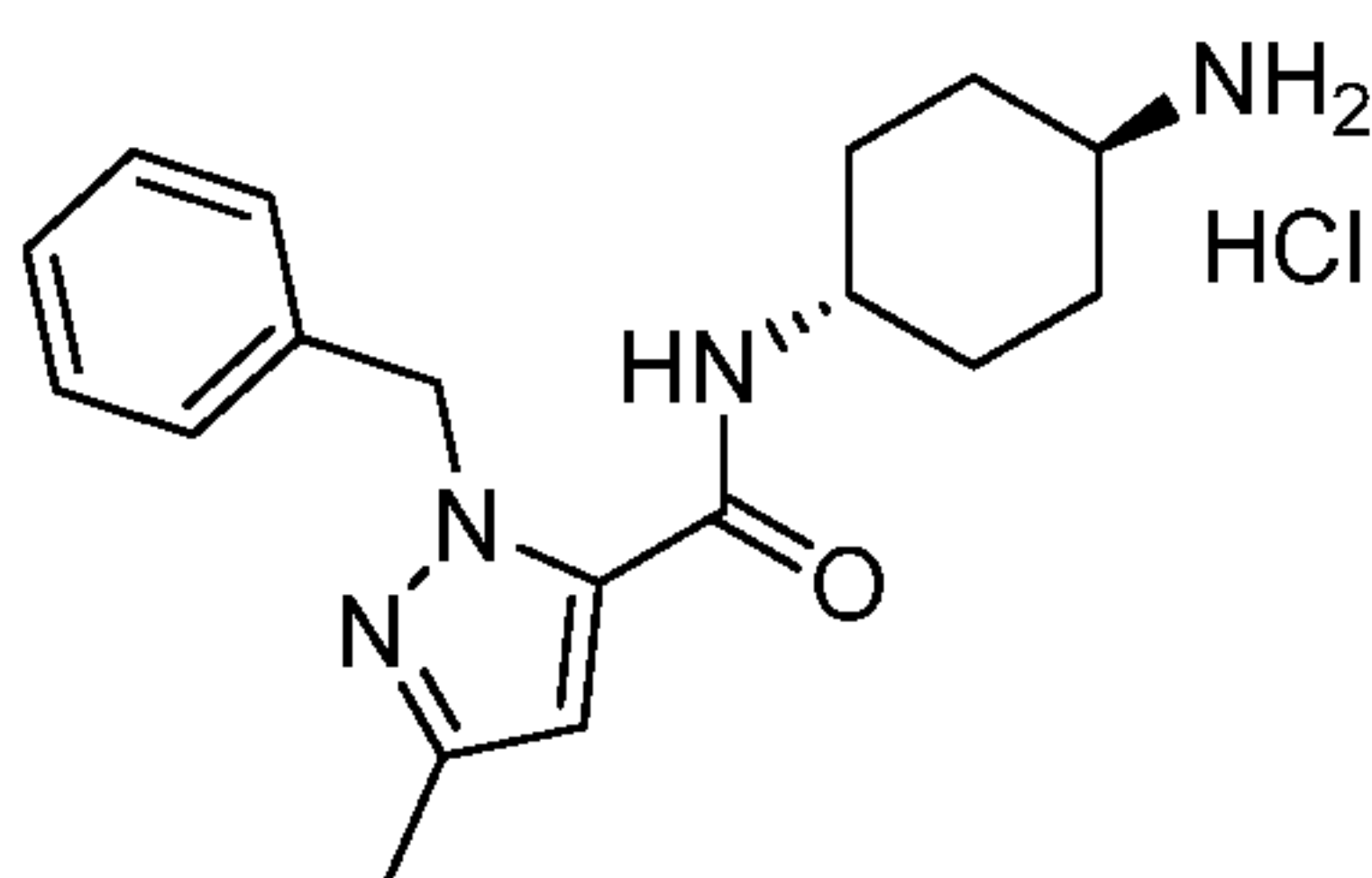
Step 4: Synthesis of N-(1-(4-aminobutanoyl)piperidin-4-yl)-1H-1,2,4-triazole-5-carboxamide



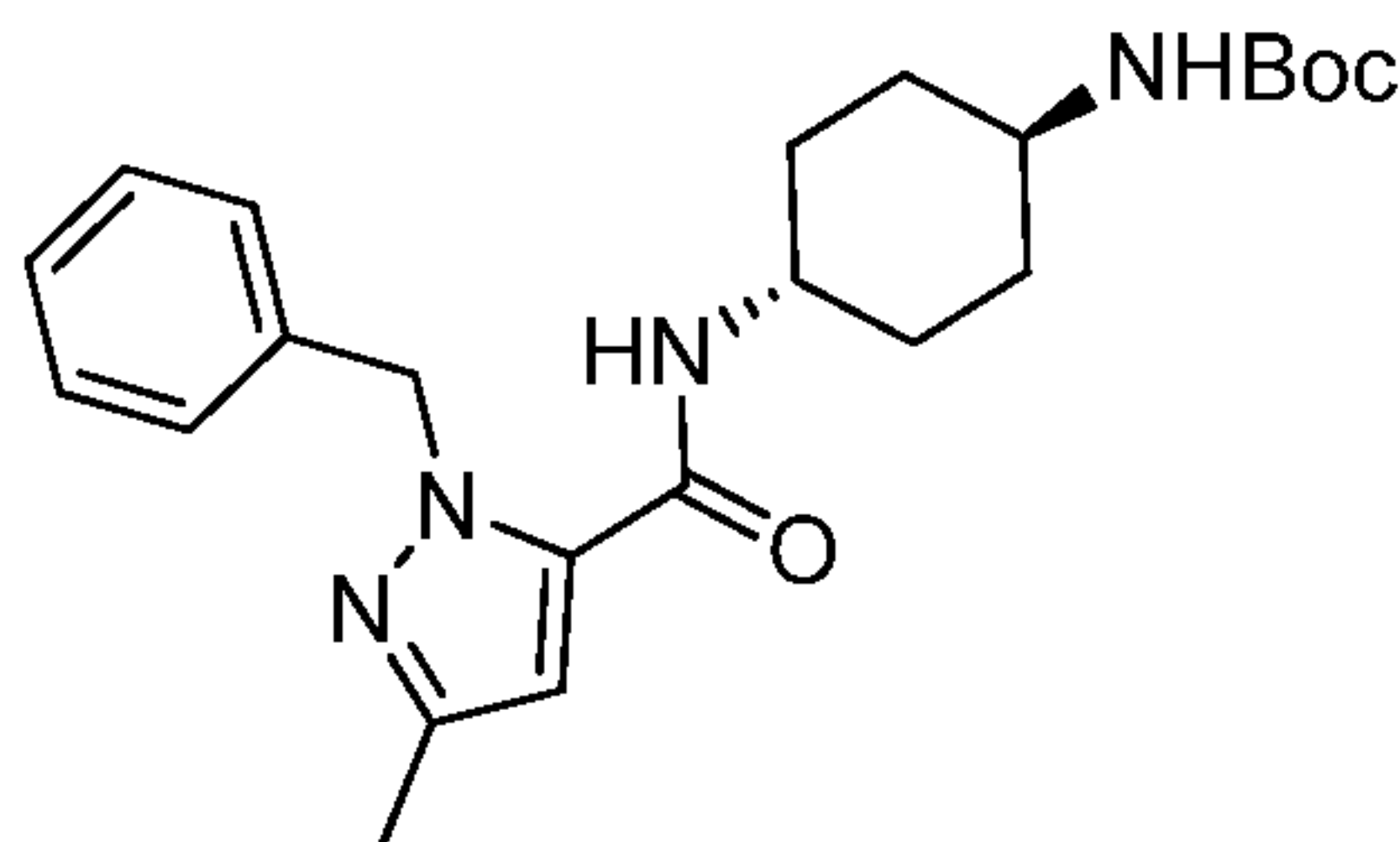
[0276] To a mixture of tert-butyl (4-(4-(1H-1,2,4-triazole-5-carboxamido)piperidin-1-yl)-4-oxobutyl)carbamate (200.00 mg, 525.71 μ mol, 1.00 Eq) in DCM (20 mL) was added TFA (5mL) dropwise at 0 $^{\circ}\text{C}$. The mixture was stirred at 0 $^{\circ}\text{C}$ for 30 min. The reaction then warmed slowly to 20 $^{\circ}\text{C}$ and stirred at this temperature for another 12 h. LCMS showed the reaction complete. The mixture was concentrated under reduced pressure at 60 $^{\circ}\text{C}$. The residue was purified by prep-HPLC to afford N-(1-(4-aminobutanoyl)piperidin-4-yl)-1H-1,2,4-triazole-5-carboxamide (104.20 mg, 50.26% yield) as colorless oil (TFA salt). ^1H NMR (400 MHz, MeOD-d_4) δ 8.49 (s, 1 H) 4.54 (d, $J = 13.55$ Hz, 1 H) 4.12-4.21 (m, 1 H) 4.00 (d, $J = 13.80$ Hz, 1 H) 3.25 (t, $J = 11.80$ Hz, 1 H) 3.02 (t, $J = 7.28$ Hz, 2 H) 2.86 (t, $J = 11.67$ Hz, 1 H) 2.60 (t, $J = 6.90$ Hz, 2 H) 1.92-2.08 (m, 4 H) 1.46-1.73 (m, 2 H); LCMS (m/z): 281.1 $[\text{M}+\text{H}]^+$.

EXAMPLE 8

Synthesis of N-((1r,4r)-4-aminocyclohexyl)-1-benzyl-3-methyl-1H-pyrazole-5-carboxamide hydrochloride (Cpd. No. 29)

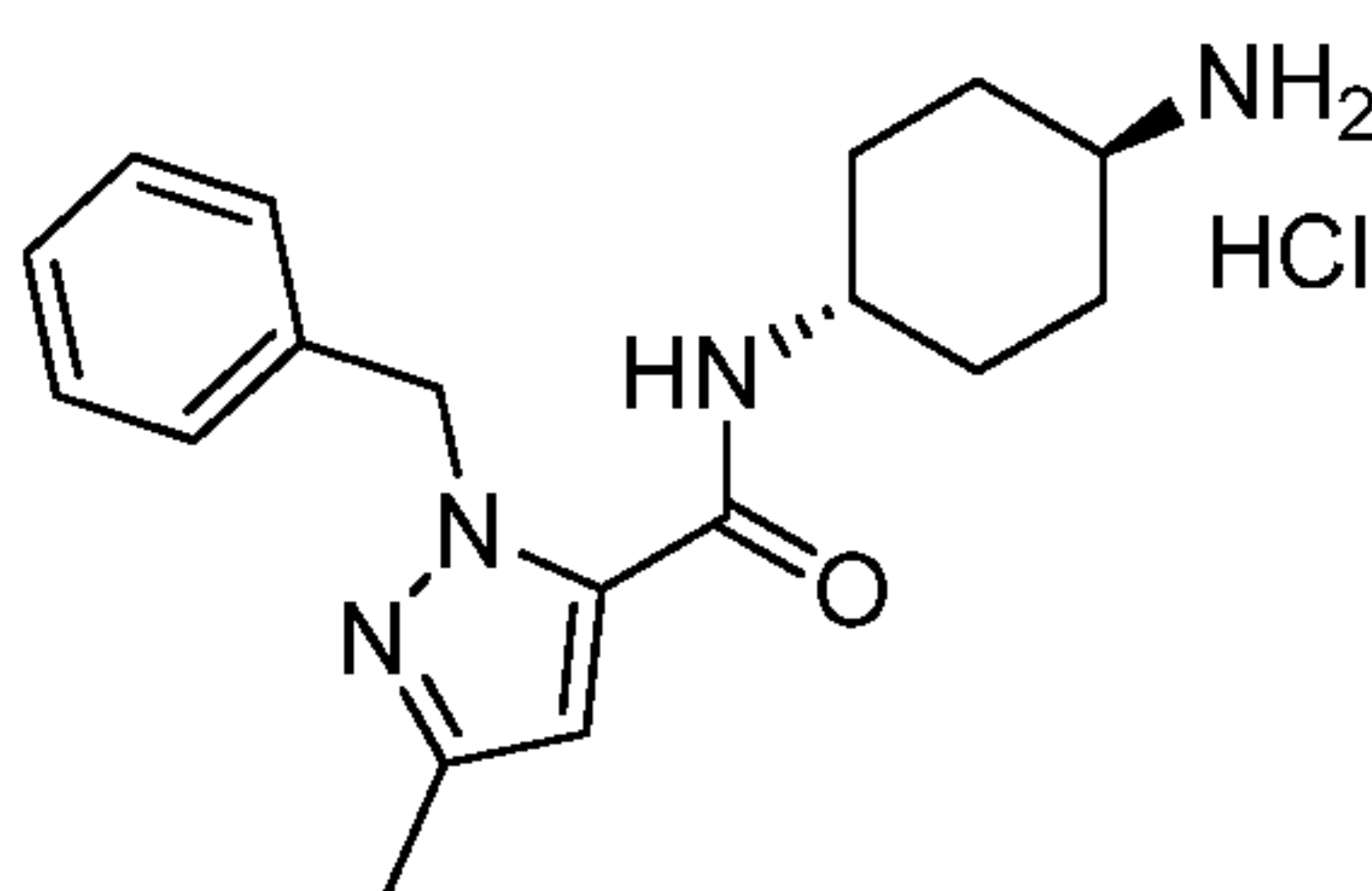


Step 1: Synthesis of tert-butyl ((1r,4r)-4-(1-benzyl-3-methyl-1H-pyrazole-5-carboxamido)cyclohexyl)carbamate



[0277] To a stirred solution of 1-benzyl-3-methyl-1H-pyrazole-5-carboxylic acid (0.150 g, 0.69 mmol) in DMF (5 mL) was added HATU (0.393 g, 1.0 mmol) and diisopropylethylamine (0.24 mL, 1.4 mmol). The solution was stirred for 10 min at 0 °C. tert-Butyl ((1r,4r)-4-aminocyclohexyl)carbamate (0.147 g, 0.69 mmol) was added and the reaction stirred at rt for 2 h. The progress of the reaction was monitored by TLC. After complete consumption of starting material, the reaction was quenched with water and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain a crude residue which was purified by column chromatography to afford tert-butyl ((1r,4r)-4-(1-benzyl-3-methyl-1H-pyrazole-5-carboxamido)cyclohexyl)carbamate (0.08 g, 25%). LCMS: 313.1 (M-100)⁺.

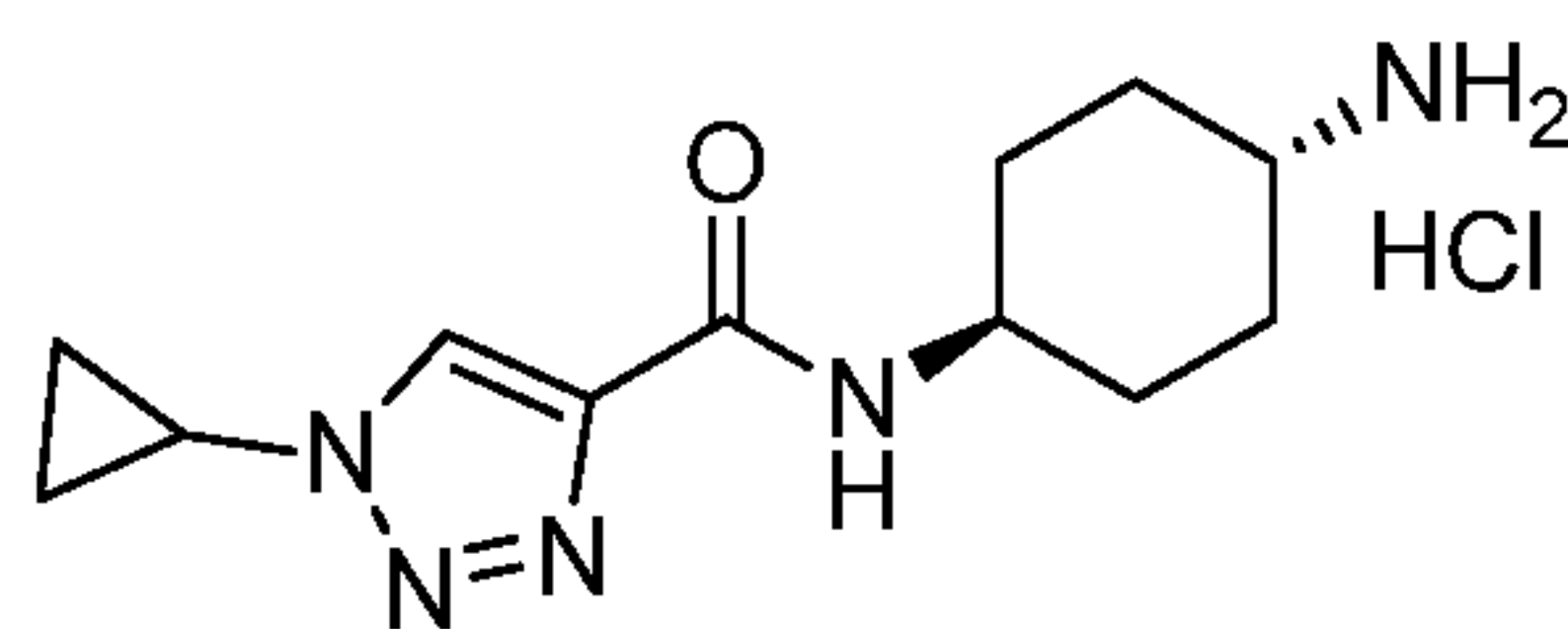
Step 2: Synthesis of N-((1r,4r)-4-aminocyclohexyl)-1-benzyl-3-methyl-1H-pyrazole-5-carboxamide hydrochloride



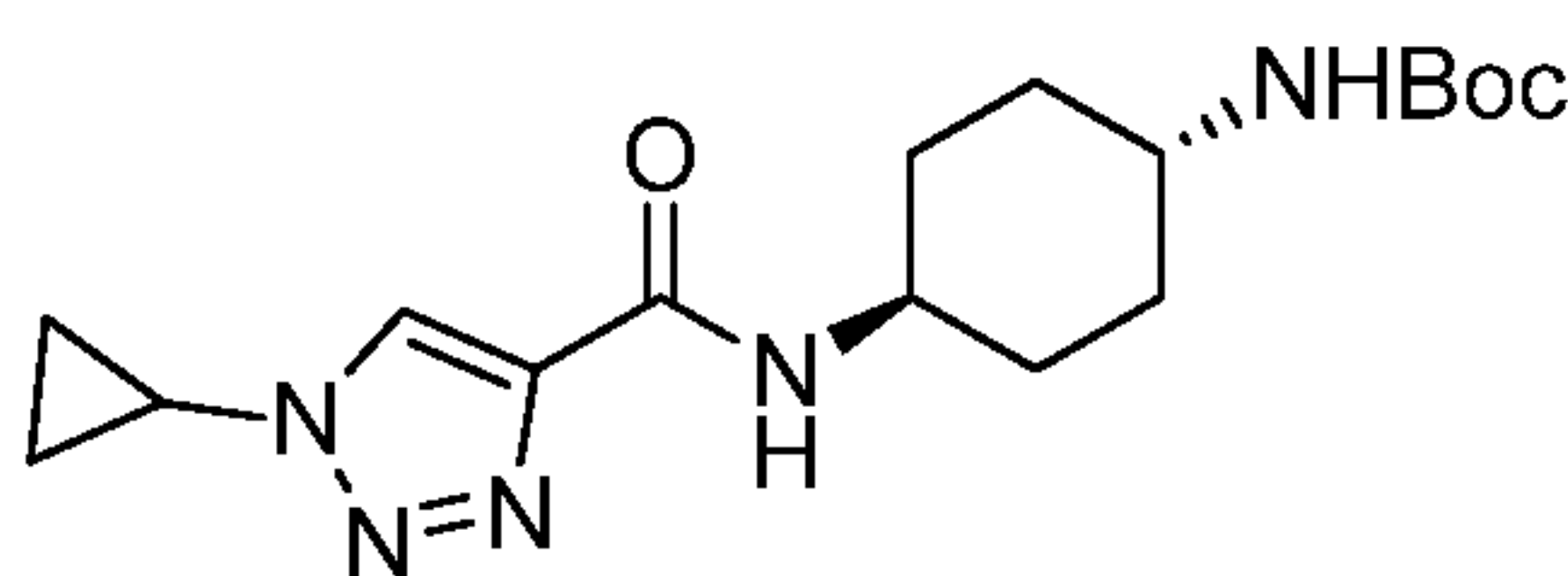
[0278] To a stirred solution of tert-butyl ((1r,4r)-4-(1-benzyl-3-methyl-1H-pyrazole-5-carboxamido)cyclohexyl)carbamate (0.05 g, 0.121 mmol) in dioxane (1 mL) at 0 °C was added 4 M dioxane:HCl (1.5 mL). The reaction mixture was stirred at rt for 1 h. The progress of the reaction was monitored by TLC. After complete consumption of the starting material, the solvent was removed under reduced pressure to obtain a crude residue. The material was purified by repeated washing with ether and pentane to obtain N-((1r,4r)-4-aminocyclohexyl)-1-benzyl-3-methyl-1H-pyrazole-5-carboxamide hydrochloride (0.03 g, 51%). ¹H NMR (400 MHz, DMSO-d₆): δ 8.26 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 5.3 Hz, 3H), 7.33-7.10 (m, 5H), 6.66 (s, 1H), 5.60 (s, 2H), 2.96 (d, *J* = 10.9 Hz, 1H), 2.16 (s, 3H), 1.96 (d, *J* = 10.4 Hz, 2H), 1.83 (d, *J* = 11.1 Hz, 2H), 1.47-1.26 (m, 4H); LCMS: 313.2 (M+H)⁺.

EXAMPLE 9

Synthesis of N-((1r,4r)-4-aminocyclohexyl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide hydrochloride

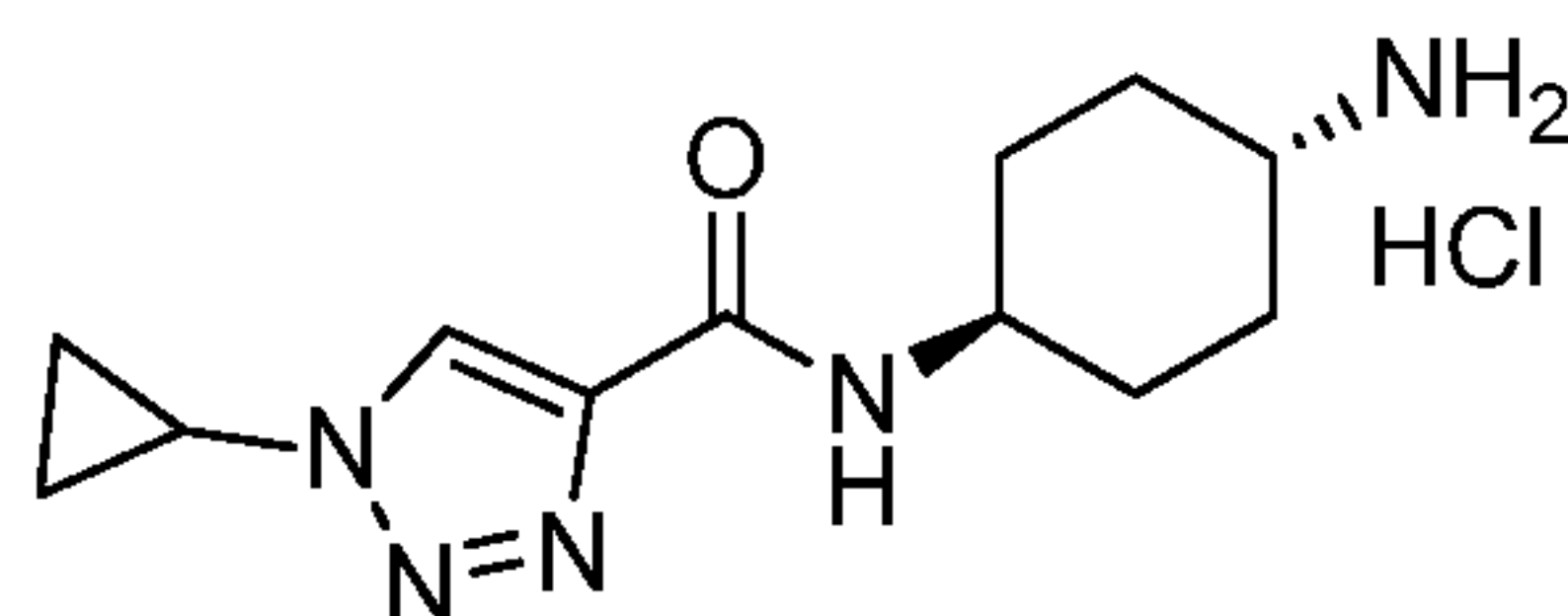


Step 1: Synthesis of tert-butyl ((1r,4r)-4-(1-cyclopropyl-1H-1,2,3-triazole-4-carboxamido)cyclohexyl)carbamate



[0279] To a stirred solution of tert-butyl ((1r,4r)-4-aminocyclohexyl)carbamate (0.090 g, 0.420 mmol) in DMF (2 mL) was added EDCI (0.096 g, 0.504 mmol), HOBT (0.068 g, 0.504 mmol) and DIPEA (0.3 mL) and the solution stirred for 10 min at 0°C. 1-cyclopropyl-1H-1,2,3-triazole-4-carboxylic acid (0.064 g, 0.420 mmol) was then added and the reaction mixture stirred at rt for 2hr. The progress of the reaction was monitored by TLC. After complete consumption of starting material, the reaction was quenched with water and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried using Na₂SO₄ and concentrated under reduced pressure to obtain a residue which was purified by column chromatography to afford tert-butyl ((1r,4r)-4-(1-cyclopropyl-1H-1,2,3-triazole-4-carboxamido)cyclohexyl)carbamate (0.035 g, 24%). LCMS: 250.1 (M-100)⁺ observed.

Step 2: Synthesis of N-((1r,4r)-4-aminocyclohexyl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide hydrochloride

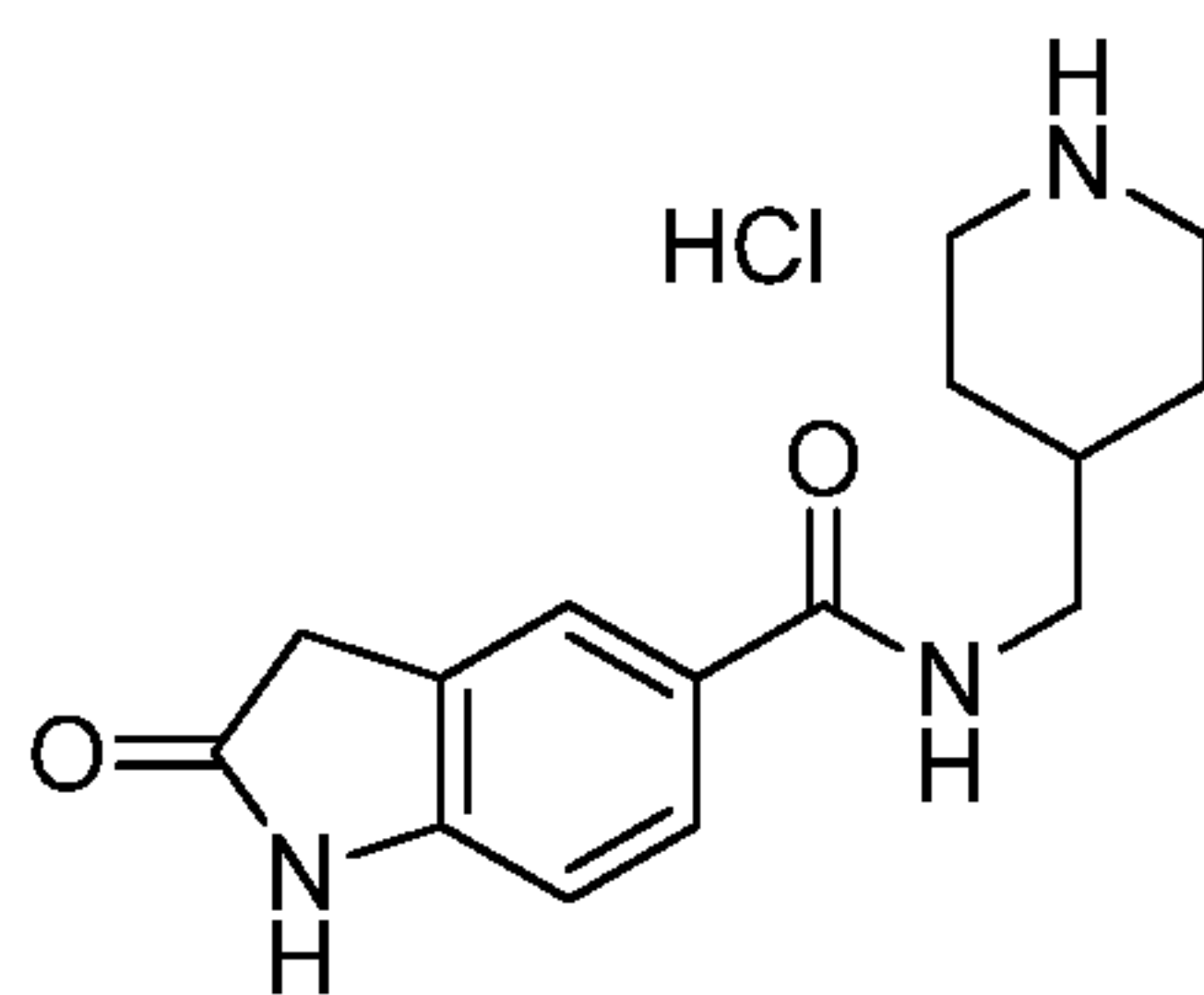


[0280] To a stirred solution of tert-butyl ((1r,4r)-4-(1-cyclopropyl-1H-1,2,3-triazole-4-carboxamido)cyclohexyl)carbamate (0.035 g, 0.10 mmol) in methanol (3 mL) was added 4M methanol:HCl (3 mL) at 0 °C and the reaction stirred at rt for 16 hr. The progress of the reaction was monitored by TLC. After complete consumption of starting material, the solvent was removed under reduced pressure and the residue was purified by washings

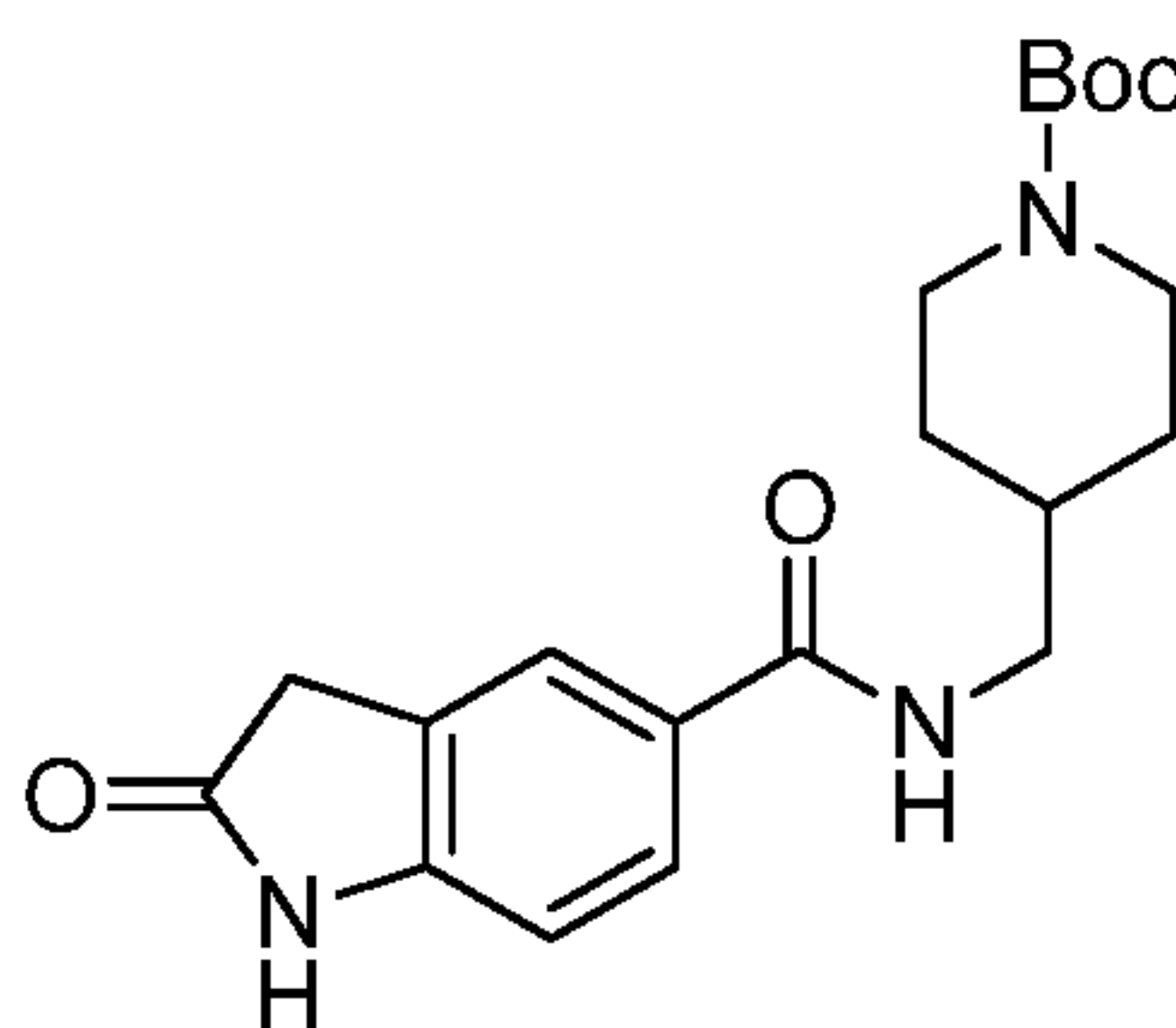
with diethyl ether and DCM to obtain N-((1*r*,4*r*)-4-aminocyclohexyl)-1-cyclopropyl-1*H*-1,2,3-triazole-4-carboxamide hydrochloride (0.013 g, 49%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.58 (s, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 7.97 (s, 2H), 4.1-4.05 (m, *J* = 7.5, 3.9 Hz, 1H), 3.75-3.66 (m, 1H), 3.01-2.88 (m, 1H), 1.97 (d, *J* = 10.5 Hz, 2H), 1.83 (d, *J* = 9.5 Hz, 2H), 1.55-1.34 (m, 4H), 1.25-1.07 (m, 4H); LCMS: 250.05 (M+H)⁺.

EXAMPLE 10

Synthesis of 2-oxo-N-(piperidin-4-ylmethyl)indoline-5-carboxamide hydrochloride (Cpd. No. 100)

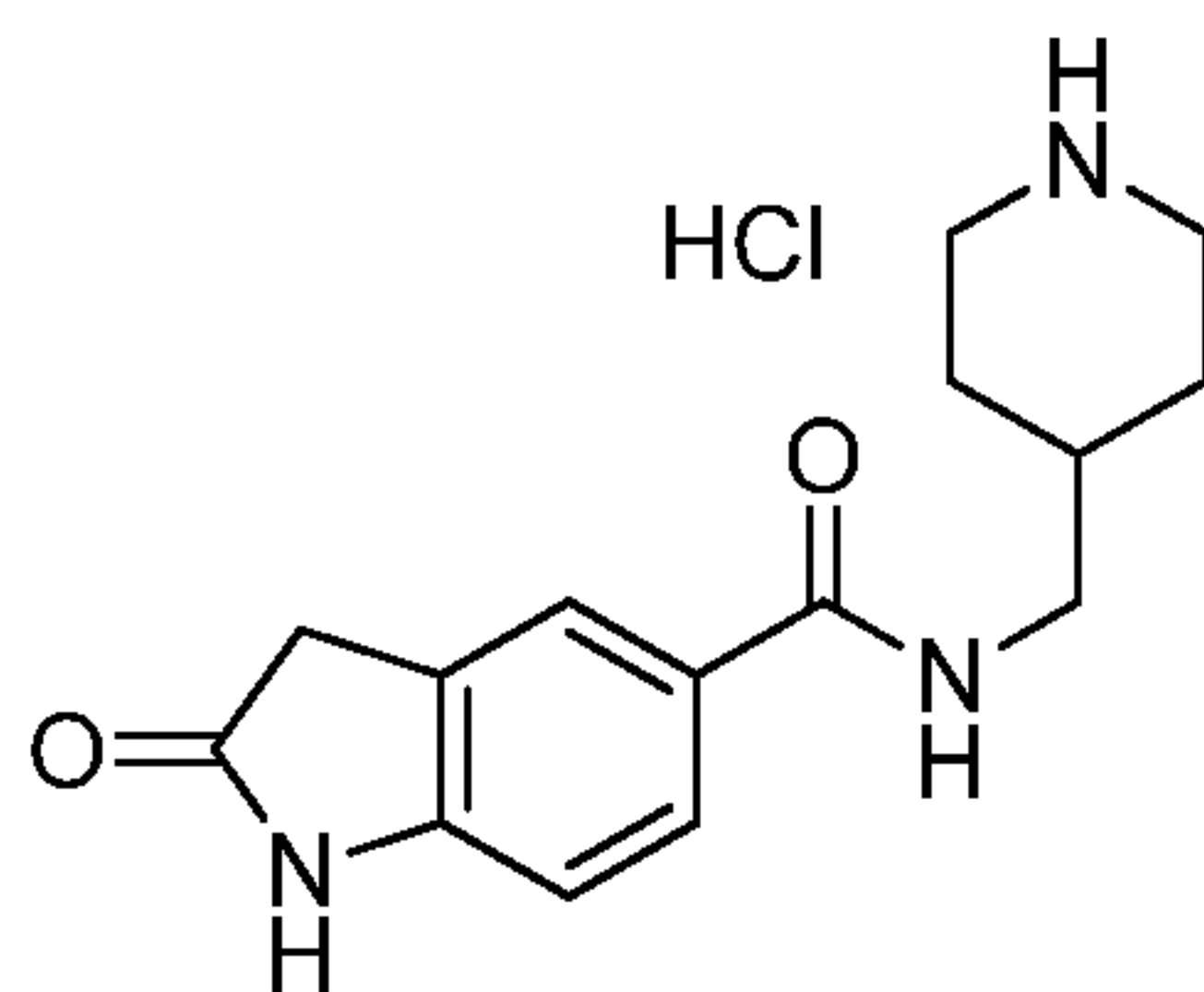


Step 1: Synthesis of tert-butyl 4-((2-oxoindoline-5-carboxamido)methyl)piperidine-1-carboxylate



[0281] To a stirred solution of 2-oxoindoline-5-carboxylic acid (0.7 g, 3.95 mmol) in DMF (5 mL) was added EDCI.HCl (1.13 g, 5.92 mmol), HOBt (0.8 g, 5.92 mmol) and triethylamine (1.7 mL, 11.8 mmol). The solution was stirred for 10 min at 0 °C. After that tert-butyl 4-(aminomethyl)piperidine-1-carboxylate (0.93 g, 4.34 mmol) was added and the reaction stirred at rt for 16 h. The progress of the reaction was monitored by TLC. After complete consumption of starting material, the reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain a crude residue which was purified by preparative HPLC to afford tert-butyl 4-((2-oxoindoline-5-carboxamido)methyl)piperidine-1-carboxylate (0.130 g, 8%) LCMS: 274.1 (M-Boc)⁺.

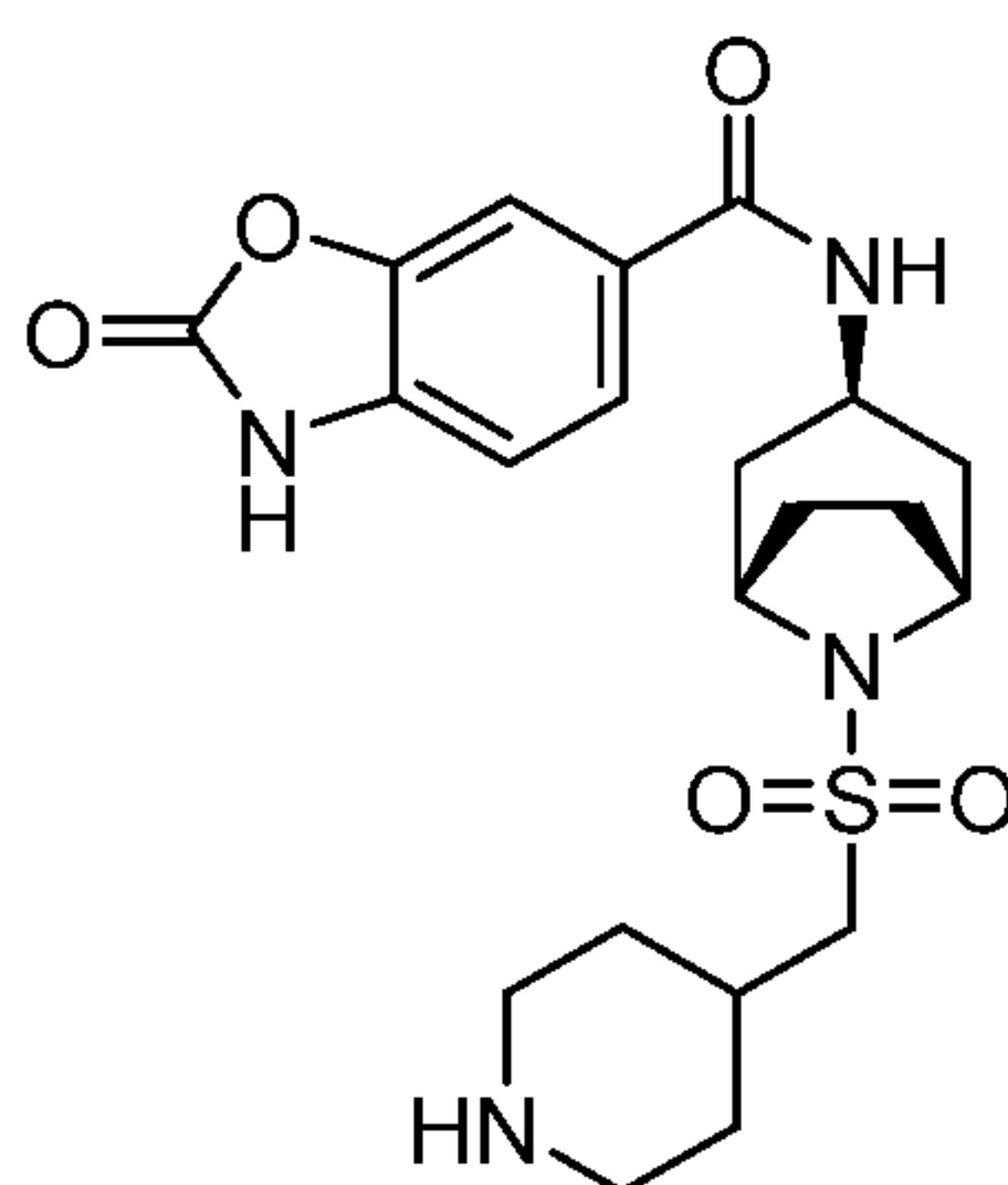
Step 2: Synthesis of 2-oxo-N-(piperidin-4-ylmethyl)indoline-5-carboxamide hydrochloride



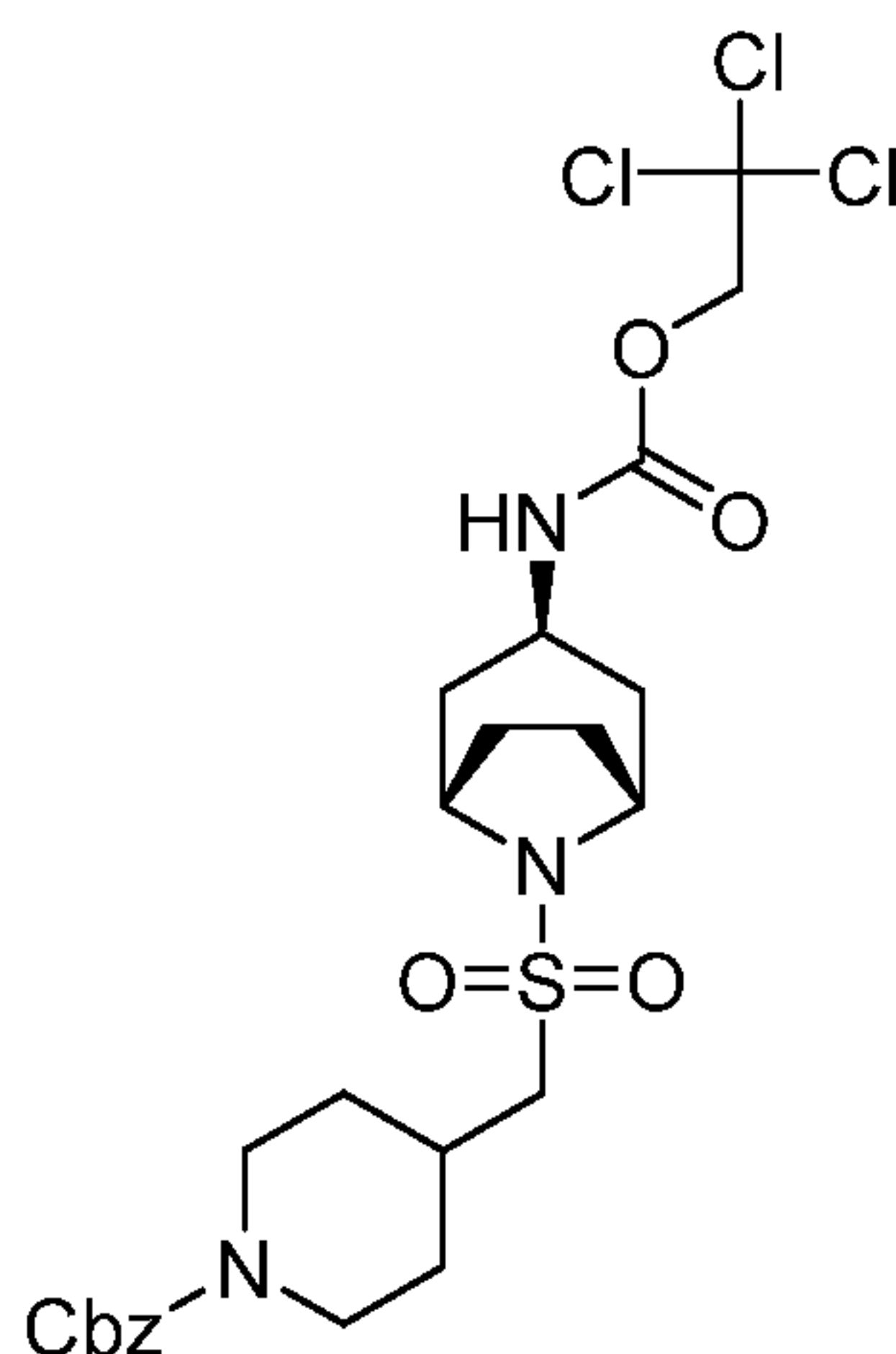
[0282] To a stirred solution of tert-butyl 4-((2-oxoindoline-5-carboxamido)methyl)piperidine-1-carboxylate (0.03 g, 0.08 mmol) in dioxane (1 mL) at 0 °C was added 4M dioxane:HCl solution (1 mL). The reaction mixture was stirred at rt for 3 h. The progress of the reaction was monitored by TLC. After complete consumption of starting material, the solvent was removed under reduced pressure to obtain a crude residue which was purified by repeated washing with ether and hexane to obtain 2-oxo-N-(piperidin-4-ylmethyl)indoline-5-carboxamide hydrochloride (0.008 g, 36%). ¹H NMR (400 MHz, DMSO-d₆): δ 10.66 (s, 1H), 8.72 (d, *J* = 12.3 Hz, 1H), 8.42 (q, *J* = 8.1, 7.1 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.1 Hz, 1H), 3.54 (s, 2H), 3.25 (d, *J* = 12.4 Hz, 2H), 3.16 (t, *J* = 6.1 Hz, 2H), 2.82 (q, *J* = 11.8 Hz, 2H), 2.62 (s, 1H), 1.79 (d, *J* = 13.4 Hz, 2H), 1.35-1.32 (m, 2H); LCMS: 274.15 (M+H)⁺.

EXAMPLE 11

Synthesis of 2-oxo-N-(((1R,3r,5SR)-8-(piperidin-4-ylmethylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-2,3-dihydrobenzo[d]oxazole-6-carboxamide hydrochloride (Cpd. No. 601)

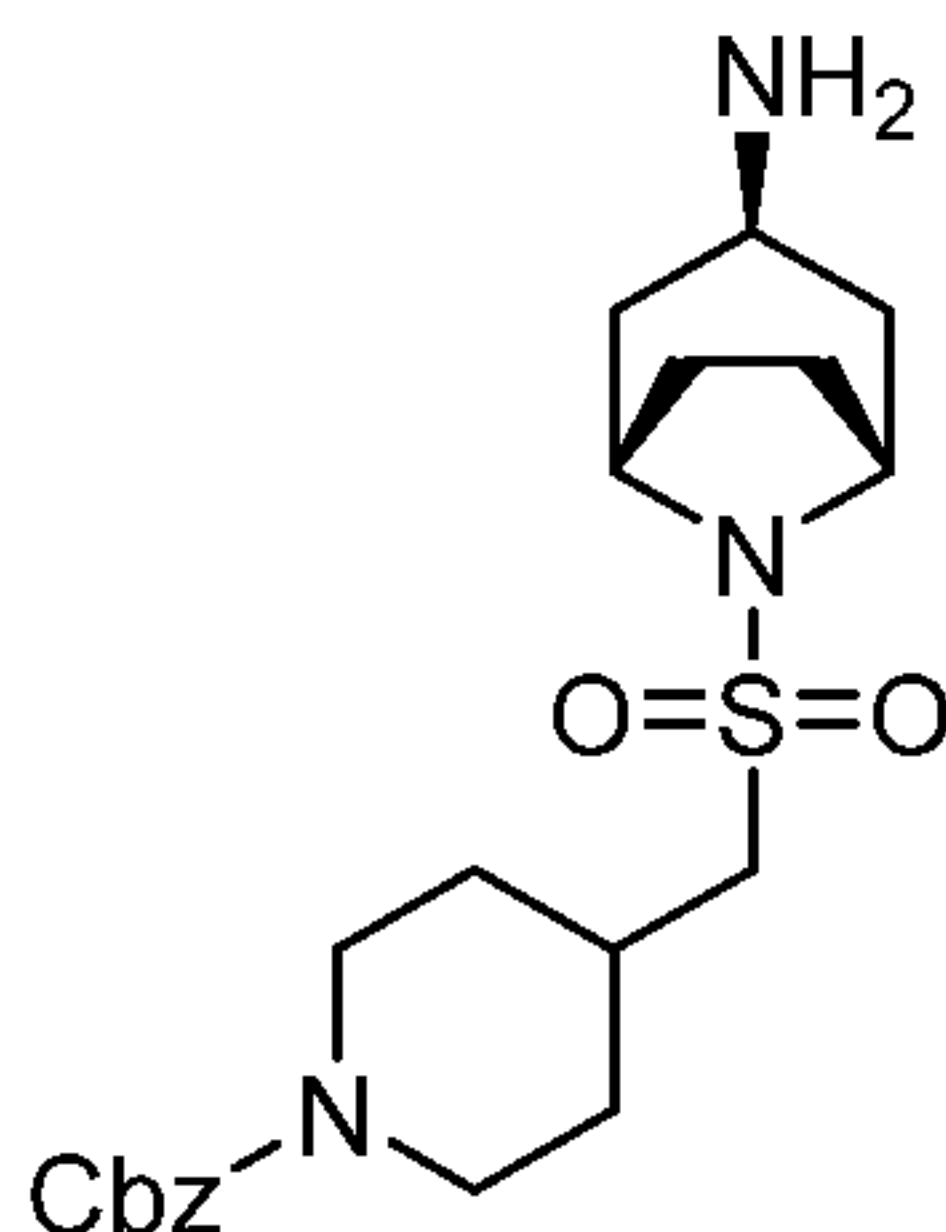


Step 1: Synthesis of benzyl 4-(((1R,3r,5S)-3-((2,2,2-trichloroethoxy)carbonylamino)-8-aza-bicyclo[3.2.1]octan-8-ylsulfonyl)methyl)piperidine-1-carboxylate



[0283] Into a 100-mL round-bottom flask was placed 2,2,2-trichloroethyl N-[(1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl]carbamate (780 mg, 2.59 mmol, 1.00 equiv), dichloromethane (10 mL), TEA (0.93 g) added dropwise at 0°C. Then benzyl 4-[(chlorosulfonyl)methyl]piperidine-1-carboxylate (1 g, 3.01 mmol, 1.17 equiv) was added in several portions. The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was chromatographed on a silica gel column with dichloromethane/methanol (20:1-10:1). This resulted in 1.3 g (84%) of benzyl 4-[[[(1R,3r,5S)-3-[[[(2,2,2-trichloroethoxy)carbonyl]amino]-8-azabicyclo[3.2.1]octane-8-sulfonyl]methyl]piperidine-1-carboxylate as a white solid. ¹H NMR (400 MHz, CDCl₃) δ : 7.41-7.32 (m, 5H), 5.32-5.10 (m, 2H), 4.48 (s, 2H), 4.27-4.12 (m, 4H), 4.00-3.96 (m, 1H), 2.93-2.80 (m, 4H), 2.30-2.07 (m, 5H), 1.98-1.91 (m, 6H), 1.30-1.26 (m, 3H) ppm. LCMS (method A, ESI): RT = 1.32 min, *m/z* = 620.2 [M+Na]⁺.

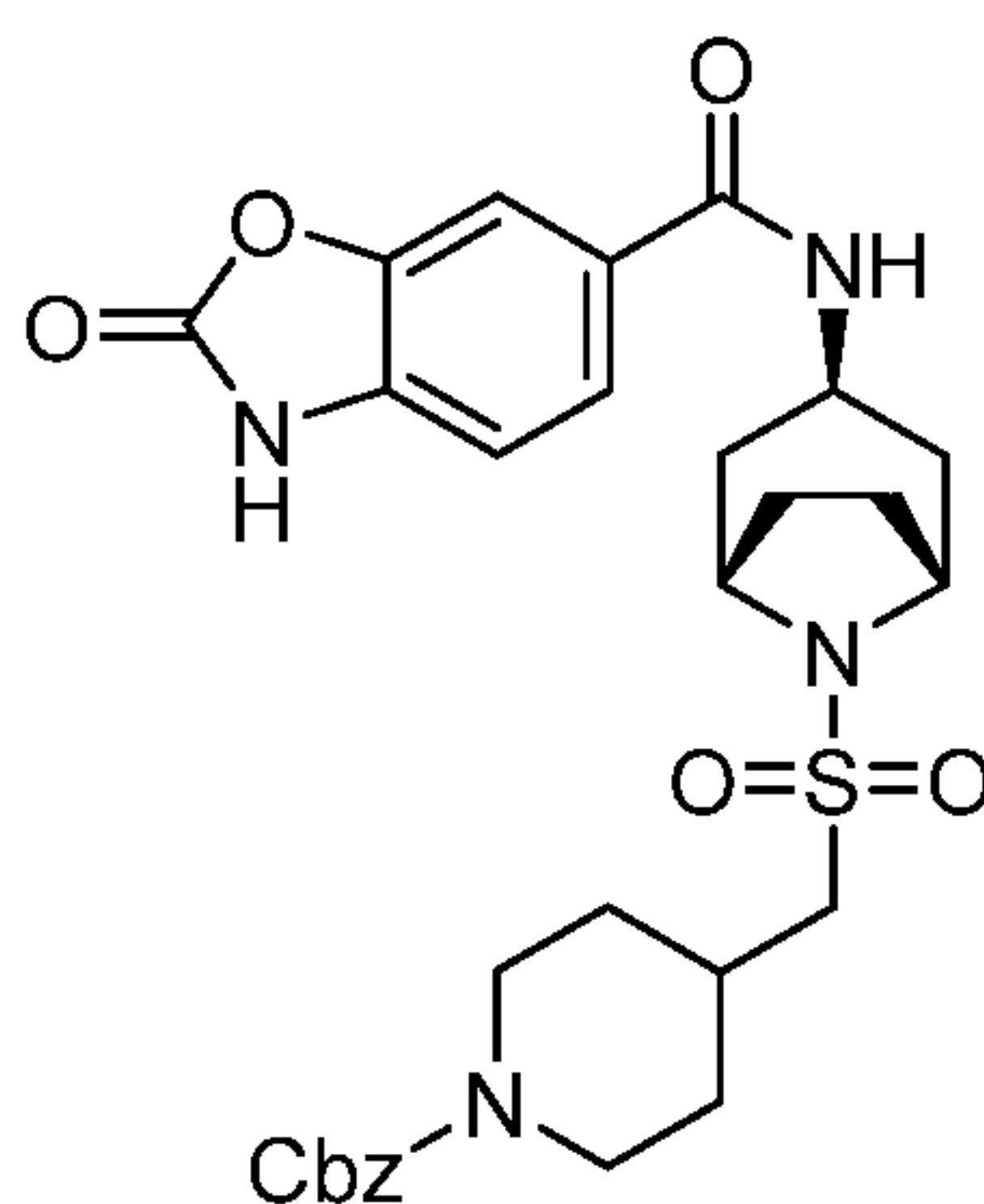
Step 2: Synthesis of benzyl 4-(((1R,3r,5S)-3-amino-8-aza-bicyclo[3.2.1]octan-8-ylsulfonyl)methyl)piperidine-1-carboxylate



[0284] Into a 100-mL round-bottom flask was placed benzyl 4-[[[(1R,3r,5S)-3-[[[(2,2,2-trichloroethoxy)carbonyl]amino]-8-azabicyclo[3.2.1]octane-8-sulfonyl]methyl]piperidine-1-carboxylate (1 g, 1.68 mmol, 1.00 equiv), acetic acid (15

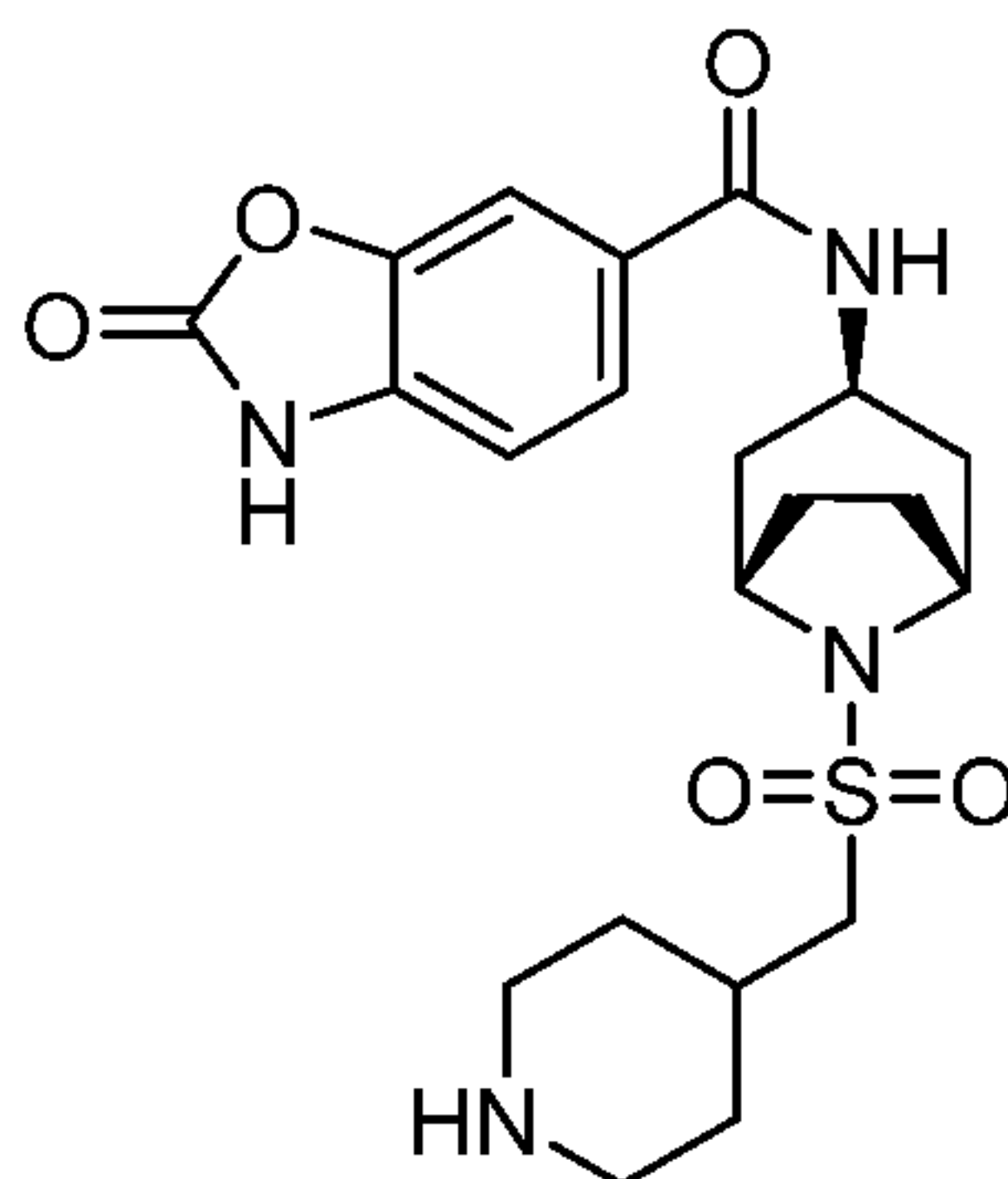
mL), water (1 mL), and zinc (1.63 g, 24.92 mmol, 14.88 equiv). The resulting mixture was stirred for 2 h at room temperature and then diluted with 30 mL of H₂O. The solids were filtered out. The pH value of the filtrate was adjusted to 9 with NaOH (40%, aq.). The resulting solution was extracted with 3x30 mL of dichloromethane and the organic layers combined, dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 0.7 g (99%) of benzyl 4-[[[(1R,3r,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-sulfonyl]methyl]piperidine-1-carboxylate as a white solid. LCMS (method D, ESI): RT = 0.85 min, m/z = 422.3 [M+H]⁺.

Step 3: Synthesis of benzyl 4-(((1R,3r,5S)-3-(2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxamido)-8-aza-bicyclo[3.2.1]octan-8-ylsulfonyl)methyl)piperidine-1-carboxylate



[0285] Into a 25-mL round-bottom flask was placed 2-oxo-2,3-dihydro-1,3-benzoxazole-6-carboxylic acid (100 mg, 0.56 mmol, 2.35 equiv), N,N-dimethylformamide (10 mL), HOBt (135 mg, 2.00 equiv) and EDCI (191 mg, 2.00 equiv). Then benzyl 4-[[[(1R,3r,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-sulfonyl]methyl]piperidine-1-carboxylate (100 mg, 0.24 mmol, 1.00 equiv) was added in several portions. After complete addition, TEA (250 mg, 5.00 equiv) was added dropwise. The resulting solution was stirred for 1 h at room temperature. The mixture was concentrated under vacuum and the residue diluted with 10 mL of H₂O. This mixture was extracted with 3x10 mL of ethyl acetate and the organic layers combined. The combined extracts were washed with 2x30 mL of brine, dried, and concentrated. The residue was chromatographed on a silica gel column with dichloromethane/methanol (10/1). This resulted in 100 mg (72%) of benzyl 4-[[[(1R,3r,5S)-3-(2-oxo-2,3-dihydro-1,3-benzoxazole-6-amido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]methyl]piperidine-1-carboxylate as yellow oil. LCMS (method D, ESI): RT = 1.38 min, m/z = 583.0 [M+H]⁺.

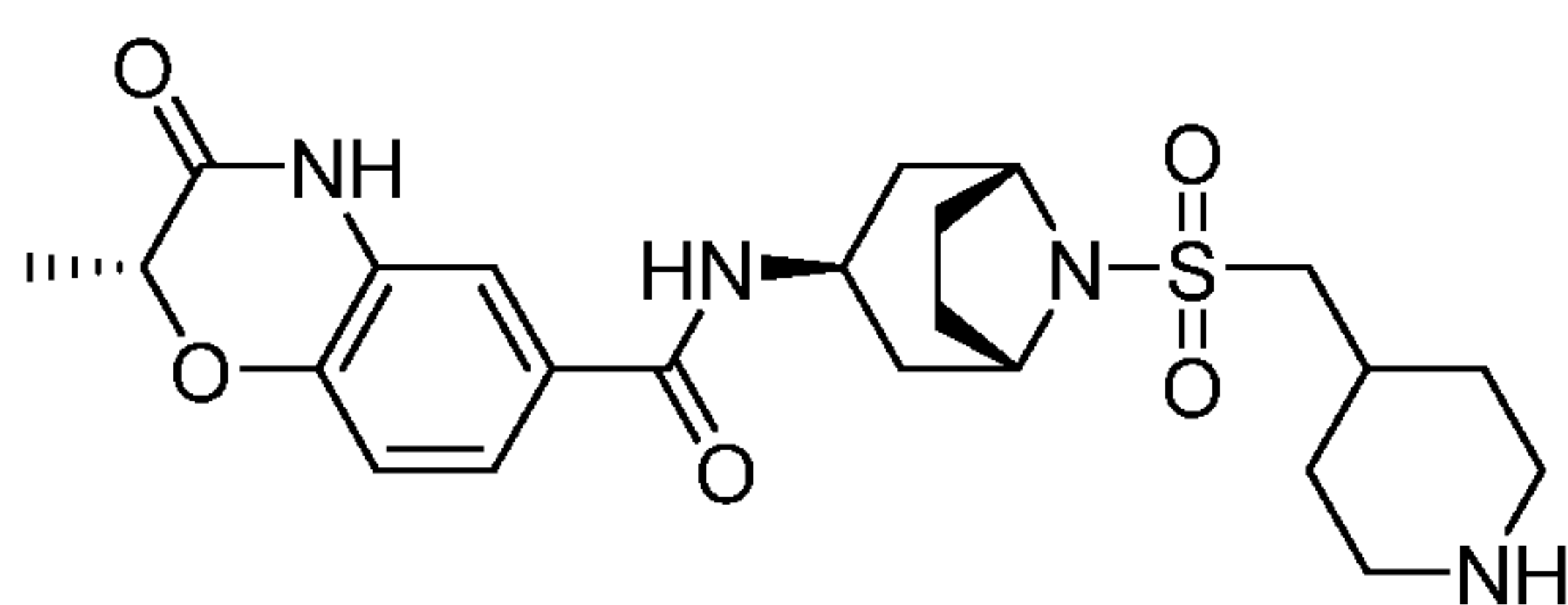
Step 4: Synthesis of 2-oxo-N-((1R,3r,5S)-8-(piperidin-4-ylmethylsulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2,3-dihydrobenzo[d]oxazole-6-carboxamide



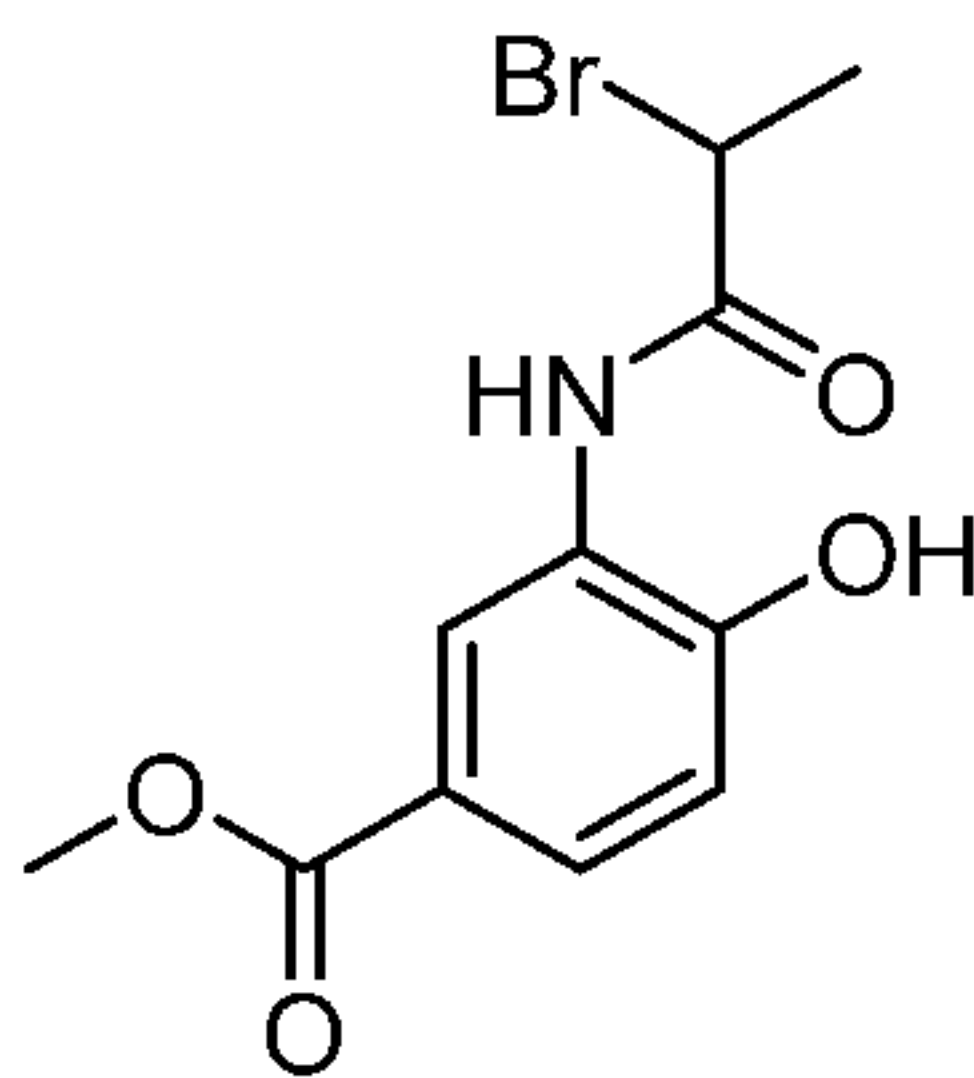
[0286] Into a 25-mL round-bottom flask was placed benzyl 4-[[[(1R,3r,5S)-3-(2-oxo-2,3-dihydro-1,3-benzoxazole-6-amido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]methyl]piperidine-1-carboxylate (100 mg, 0.17 mmol, 1.00 equiv) and hydrochloric acid (12N, 10 mL). The resulting solution was stirred for 4 h at room temperature and then concentrated under vacuum. The residue was applied onto Pre-HPLC with the following conditions: Column: X Bridge C18, 19*150 mm, 5 um; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 30%B to 70%B in 10 min; 254nm. The product was dissolved again into hydrochloric acid (5 mL, 12 N) and concentrated under vacuum. This resulted in 7.3 mg (9%) of 2-oxo-N-[(1R,3r,5S)-8-[(piperidin-4-ylmethane)sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-2,3-dihydro-1,3-benzoxazole-6-carboxamide as a white solid. ¹H NMR (300 MHz, D₂O) δ : 7.52-7.49 (m, 2H), 7.18-7.16 (m, 1H), 4.21 (s, 2H), 4.08-4.03 (m, 1H), 3.38-3.34 (m, 2H), 3.20-3.18 (m, 2H), 3.02-2.93 (m, 2H), 2.24-1.94 (m, 11H), 1.54-1.51 (m, 2H) ppm. LCMS (method D, ESI): RT = 1.65 min, *m/z* = 449.2 [M-HCl+H]⁺.

EXAMPLE 12

Synthesis of (2R)-2-methyl-3-oxo-N-[(1R,3r,5S)-8-[(piperidin-4-ylmethane)sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide hydrochloride (Cpd. No. 625)

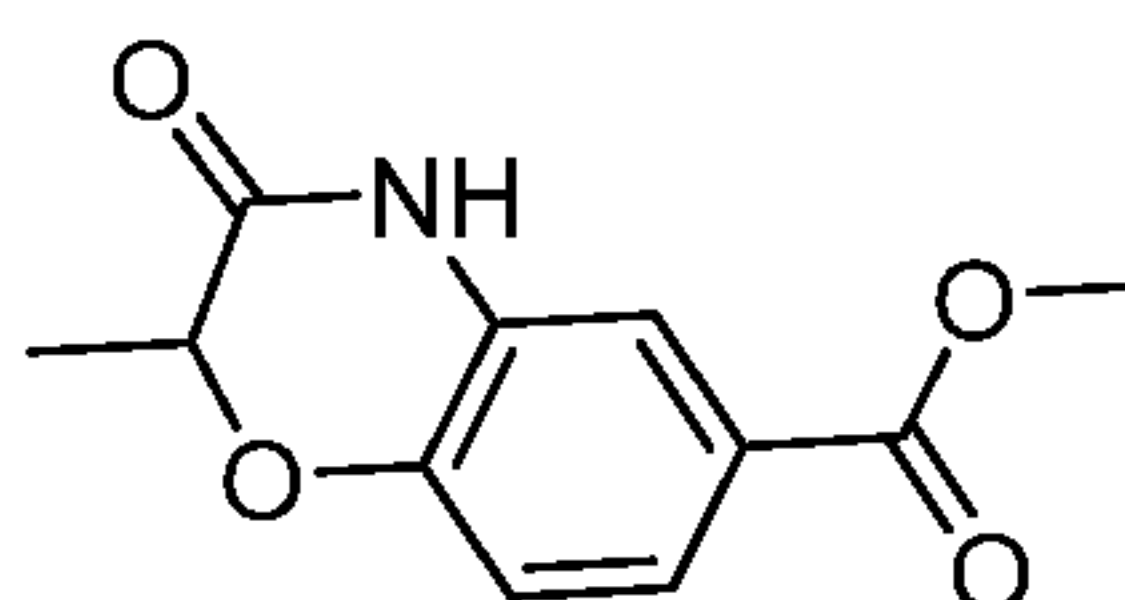


Step 1: Synthesis of methyl 3-(2-bromopropanamido)-4-hydroxybenzoate



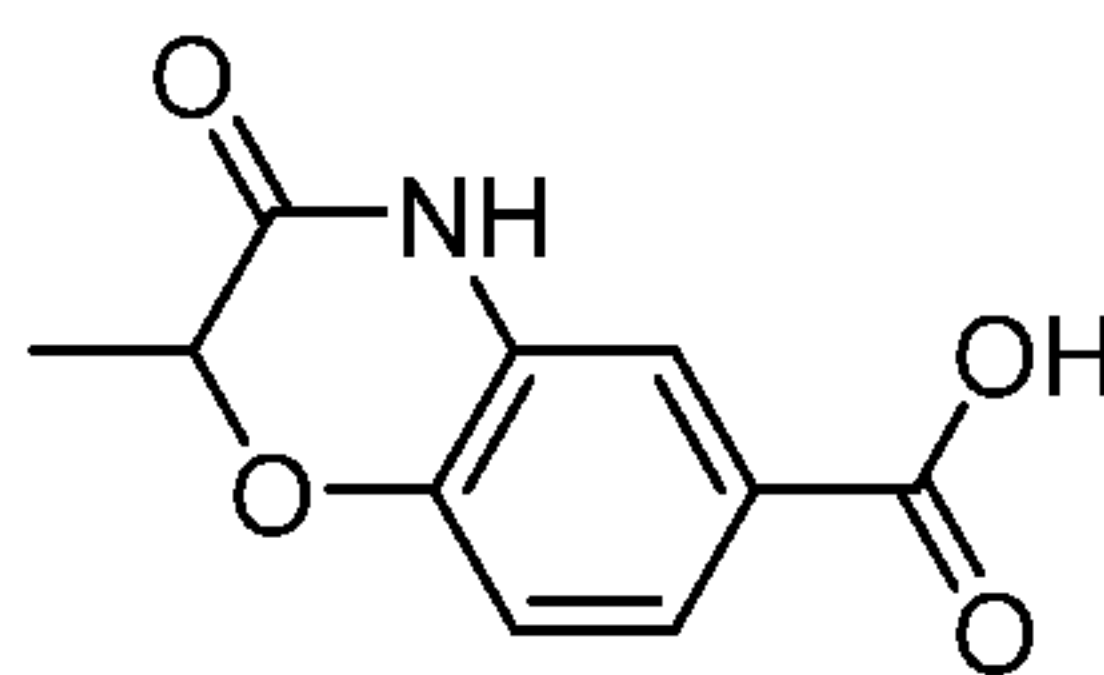
[0287] Into a 100-mL round-bottom flask was placed ethyl acetate (10 mL), water (10 mL), methyl 3-amino-4-hydroxybenzoate (1 g, 5.98 mmol, 1.00 equiv), and sodium bicarbonate (553 mg, 1.10 equiv). This was followed by the addition 2-bromopropanoyl bromide (1.3 g, 6.02 mmol, 1.00 equiv) which was added dropwise with stirring at 0°C. The resulting solution was stirred for 30 min at room temperature. The mixture was then washed with 2x30 mL of H₂O and 1x30 mL of brine. The mixture was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. This resulted in 1.5 g (83%) of methyl 3-(2-bromopropanamido)-4-hydroxybenzoate as a brown solid. ¹H NMR (300 MHz, CDCl₃) δ : 8.89 (s, 1H), 8.43 (s, 1H), 7.89-7.82 (m, 2H), 7.04 (d, *J*=8.4Hz, 1H), 4.65 (q, *J*=14.1Hz, 1H), 3.07 (s, 3H), 2.01 (d, *J*=7.2Hz, 3H) ppm. LCMS (method D, ESI): RT = 1.30min, *m/z* = 302.0 [M+H]⁺.

Step 2: Synthesis of methyl 2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxylate



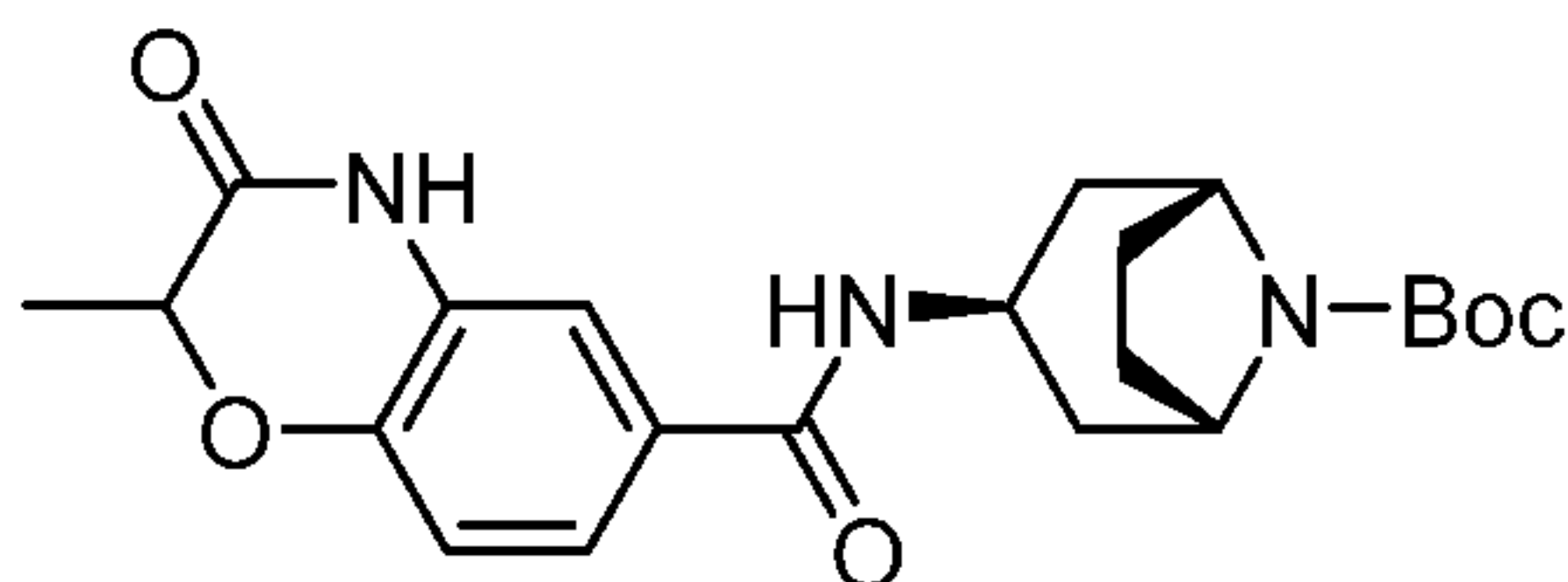
[0288] Into a 100-mL round-bottom flask was placed N,N-dimethylformamide (10 mL), methyl 3-(2-bromopropanamido)-4-hydroxybenzoate (1.5 g, 4.96 mmol, 1.00 equiv), and potassium carbonate (880 mg, 1.30 equiv). The resulting mixture was stirred for 15 h at room temperature. The mixture was then diluted with 30 mL of H₂O. The solids were collected by filtration. This resulted in 1 g (91%) of methyl 2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxylate as a brown solid. ¹H NMR (400 MHz, CDCl₃) δ : 8.29 (s, 1H), 7.72 (q, *J*=8.4Hz, 1H), 7.56 (d, *J*=2Hz, 1H), 7.03 (d, *J*=8.4Hz, 1H), 4.77 (q, *J*=14Hz, 1H), 3.93 (s, 3H), 1.64 (d, *J*=7.2Hz, 3H) ppm. LCMS (method C, ESI): RT =0.96 min, *m/z* = 222.0 [M+H]⁺.

Step 3: Synthesis of 2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxylic acid



[0289] Into a 100-mL round-bottom flask was placed tetrahydrofuran (15 mL), methanol (15 mL), water (10 mL), and methyl 2-methyl-3-oxo-3,4-dihydro-2H-1,4-benzo[b][1,4]oxazine-6-carboxylate (1 g, 4.52 mmol, 1.00 equiv). This was followed by the addition of a solution of sodium hydroxide (362 mg, 2.00 equiv) in 5 mL H₂O which was added dropwise with stirring at 0°C. The resulting solution was stirred for 10 min at 0°C in an ice/salt bath. The resulting solution was allowed to react, with stirring, for an additional 15 h at room temperature. The reaction mixture was concentrated under vacuum. The residue was diluted with 30 mL of H₂O and the pH adjusted to 3-4 with hydrochloric acid (1 N). The solids were collected by filtration. This resulted in 900 mg (96%) of 2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxylic acid as a white solid. ¹H NMR (400 MHz, CD₃OD) δ : 7.68 (q, *J*=8.4 Hz, 1H), 7.59 (d, *J*= 2 Hz, 1H), 4.47 (s, 1H), 7.03 (d, *J*= 8.4 Hz, 1H), 4.75 (q, *J*= 13.6 Hz, 1H), 1.55 (d, *J*=6.8 Hz, 3H) ppm. LCMS (method A, ESI): RT =1.08 min, *m/z* =208.0 [M+H]⁺.

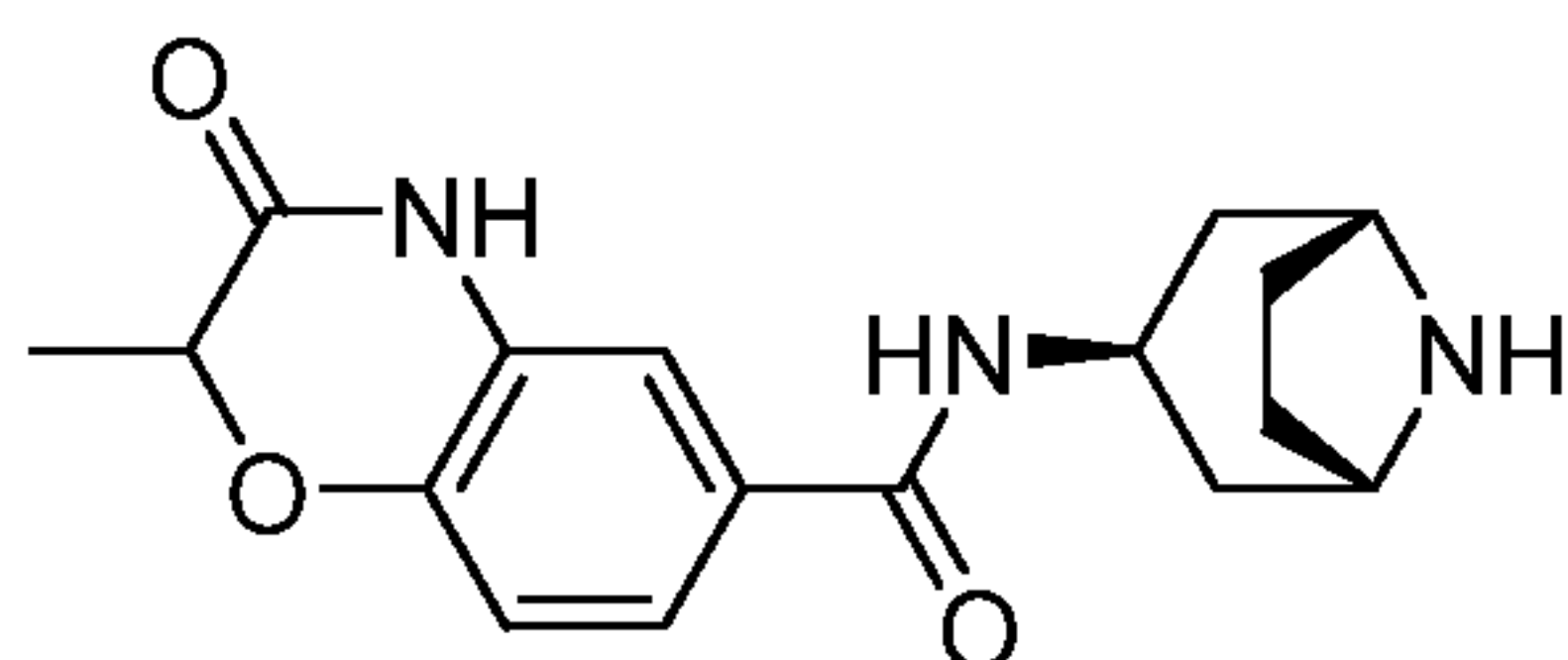
Step 4: Synthesis of tert-butyl (1R,3r,5S)-3-(2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamido)-8-azabicyclo[3.2.1]octane-8-carboxylate



[0290] Into a 100-mL round-bottom flask was placed N,N-dimethylformamide (50 mL), 2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxylic acid (500 mg, 2.41 mmol, 1.00 equiv), EDCI (923 mg, 2.00 equiv), HOBT (652 mg, 2.00 equiv), and tert-butyl (1R,3r,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (710 mg, 3.14 mmol, 1.30 equiv). This was followed by the addition of TEA (1232 mg, 5.0 equiv) which was added dropwise with stirring at 0°C. The resulting solution was stirred for 14 h at room temperature. The reaction mixture was then diluted with 50 mL of EA. The resulting mixture was washed with 3x30 mL of H₂O and 1x30 mL of brine. The mixture was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (4:1). This resulted in 800 mg (80%) of tert-butyl (1R,3r,5S)-3-(2-methyl-3-oxo-3,4-dihydro-2H-

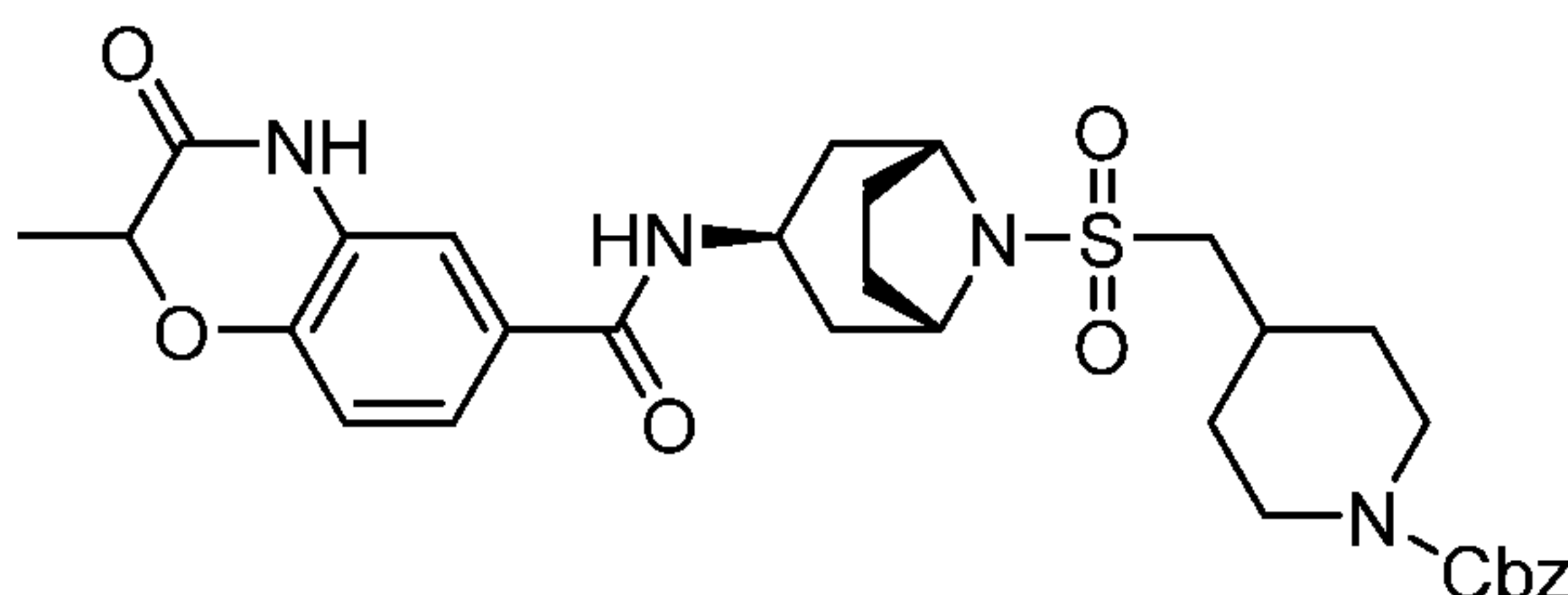
benzo[b][1,4]oxazine-6-carboxamido)-8-azabicyclo[3.2.1]octane-8-carboxylate as a white solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.66 (s, 1H), 7.52 (d, $J=1.6\text{Hz}$, 1H), 7.22 (q, $J=8.4\text{Hz}$, 1H), 7.02 (d, $J=8.4\text{Hz}$, 1H), 6.51 (d, $J=6.8\text{Hz}$, 1H), 4.72 (q, $J=13.6\text{Hz}$, 1H), 4.39-4.20 (m, 3H), 2.45-2.25 (m, 2H), 2.20-2.10 (m, 2H), 1.95-1.75 (m, 4H), 1.60 (d, $J=7.2\text{Hz}$, 3H), 1.50 (s, 9H) *ppm*. LCMS (method C, ESI): RT = 1.08 min, $m/z = 416.0$ $[\text{M}+\text{H}]^+$.

Step 5: Synthesis of N-[(1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl]-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide



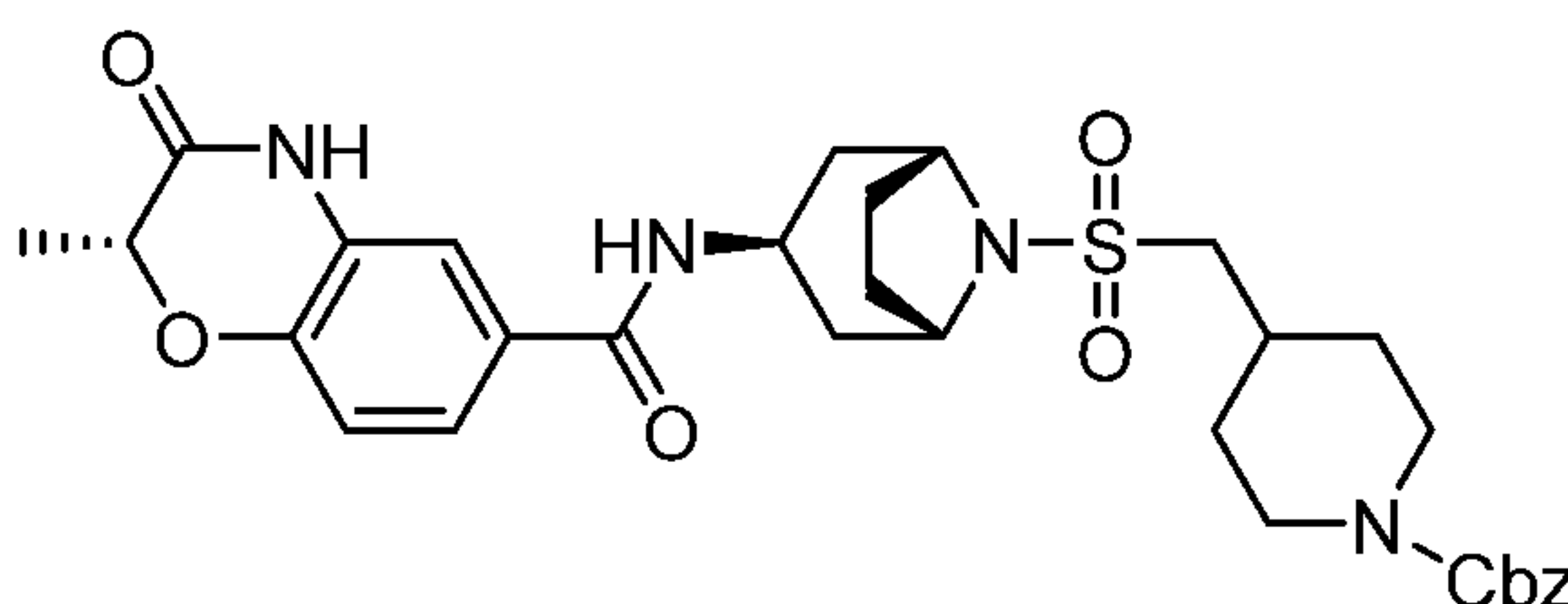
[0291] Into a 100-mL round-bottom flask was placed dichloromethane (20 mL) and tert-butyl (1R,3r,5S)-3-(2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamido)-8-azabicyclo[3.2.1]octane-8-carboxylate (800 mg, 1.93 mmol, 1.00 equiv). To the above, hydrogen chloride (gas) was introduced. The resulting solution was stirred for 4 h at room temperature and then was concentrated under vacuum. The residue was diluted with 40 mL of H_2O . The pH was adjusted to 8 with saturated aqueous sodium carbonate and the resulting mixture extracted with 3x40 mL of DCM. The organic layers were combined and washed with 2x40 mL of brine. The extract was concentrated under vacuum. This resulted in 500 mg (82%) of N-[(1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl]-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide as a light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ : 7.42 (q, $J=8.4\text{Hz}$, 1H), 7.37 (d, $J=2\text{Hz}$, 1H), 7.04 (d, $J=8.4\text{Hz}$, 1H), 4.72 (q, $J=13.6\text{Hz}$, 1H), 4.12 (t, $J=6.4\text{Hz}$, 1H), 3.69 (s, 2H), 2.22-2.15 (m, 4H), 2.10-1.95 (m, 4H), 1.54 (d, $J=6.8\text{Hz}$, 3H) *ppm*. LCMS (method A, ESI): RT = 0.93 min, $m/z=364.0$ $[\text{M}+\text{H}]^+$.

Step 6: Synthesis of benzyl 4-[[[(1R,3r,5S)-3-(2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]methyl]piperidine-1-carboxylate



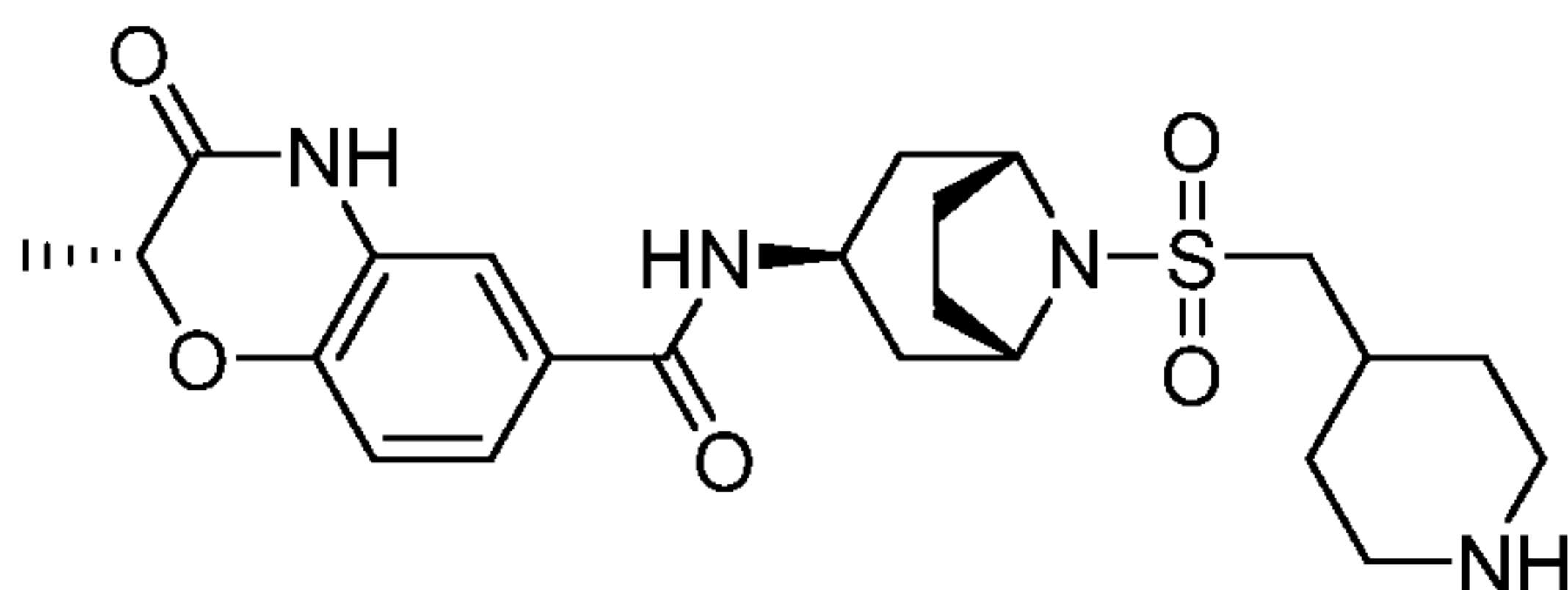
[0292] Into a 100-mL 3-necked round-bottom flask was placed N,N-dimethylformamide (10 mL), N-[(1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl]-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide (250 mg, 0.79 mmol, 1.00 equiv), and TEA (231 mg, 3.00 equiv). This was followed by the addition of a solution of benzyl 4-[(chlorosulfonyl)methyl]piperidine-1-carboxylate (657 mg, 1.98 mmol, 2.50 equiv) in 2 mL N,N-dimethylformamide which was added dropwise with stirring at -20°C. The resulting solution was stirred for 30 min at -20°C. The mixture was allowed to react, with stirring, for an additional 15 h at room temperature. The mixture was diluted with 50 mL of EA and washed with 2x20 mL of water and 2x20 mL of brine. The organic phase was dried over anhydrous sodium sulfate and filtered. The residue was chromatographed on a silica gel column with dichloromethane/methanol (20:1). This resulted in 60 mg (12%) of benzyl 4-[[[(1R,3r,5S)-3-(2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]methyl]piperidine-1-carboxylate as a white solid. LCMS (method B, ESI): RT = 1.43 min, m/z = 611.0 $[M+H]^+$.

Step 7: Synthesis of benzyl 4-[[[(1R,3r,5S)-3-[(2R)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-amido]-8-azabicyclo[3.2.1]octane-8-sulfonyl]methyl]piperidine-1-carboxylate



[0293] Benzyl 4-[[[(1R,3r,5S)-3-(2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]methyl]piperidine-1-carboxylate (60 mg) was purified by Chiral-Prep-HPLC with the following conditions (Chiral_HPLC): Column, CHIRALPAK IA; mobile phase, MTBE: EtOH = 50:50; Detector, 254nm. This resulted in 28 mg (47%) of benzyl 4-[[[(1R,3r,5S)-3-[(2R)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamido]-8-azabicyclo[3.2.1]octane-8-sulfonyl]methyl]piperidine-1-carboxylate as a white solid. ee value: 100%

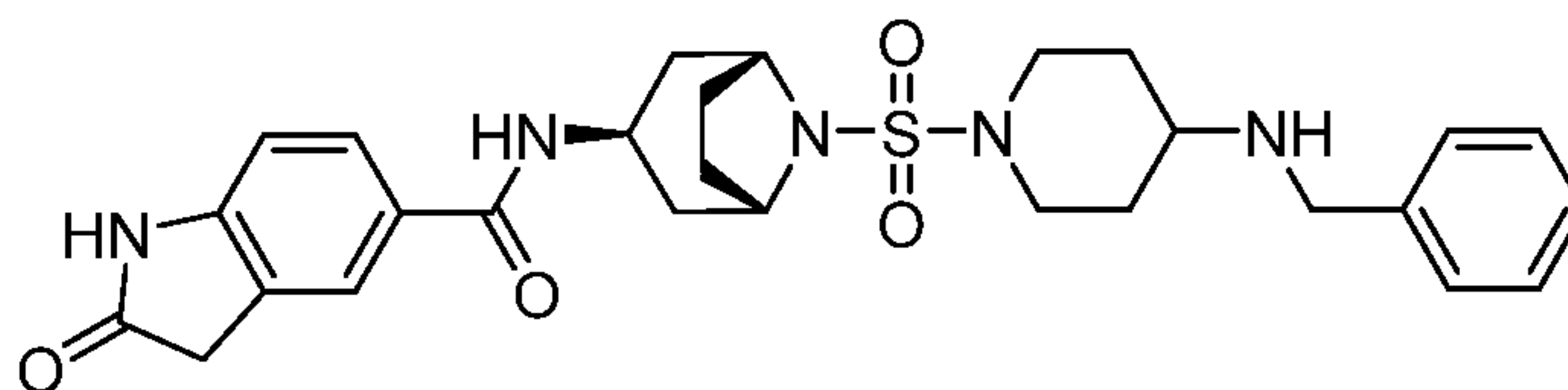
Step 8: Synthesis of (2R)-2-methyl-3-oxo-N-[(1R,3r,5S)-8-[(piperidin-4-ylmethane)sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide hydrochloride



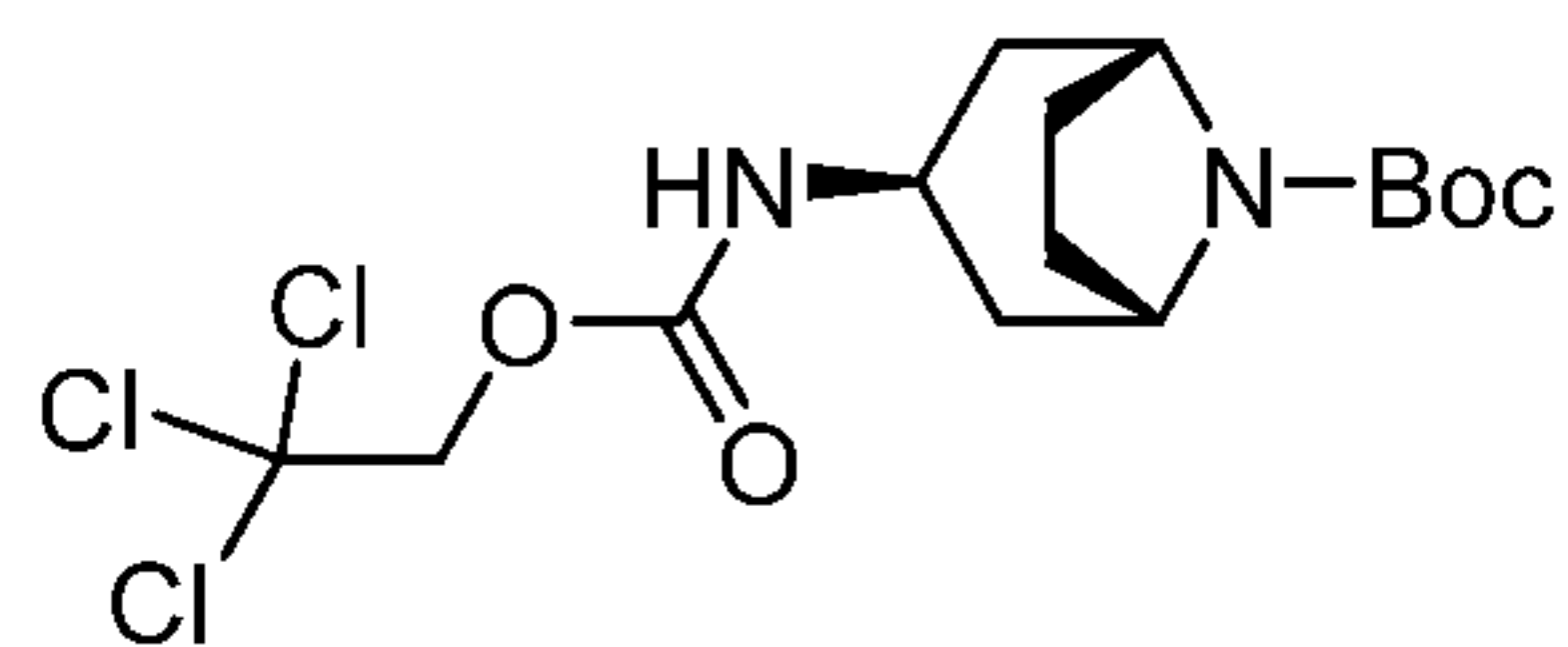
[0294] Into a 50-mL round-bottom flask was placed benzyl 4-[[[(1R,3r,5S)-3-[(2R)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamido]-8-azabicyclo[3.2.1]octane-8-sulfonyl]methyl]piperidine-1-carboxylate (28 mg, 0.05 mmol, 1.00 equiv) and hydrochloric acid (12N, 10 mL). The resulting solution was stirred for 4 h at room temperature. The resulting mixture was washed with 2x10 mL of DCM and the aqueous layer concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Prep_HPLC_MC5): Column, X Select C18, 19*250 mm, 5 um; mobile phase, Water/0.05% TFA, Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 23% B to 42% B in 11.5 min; Detector, 254nm. The resulting fractions were concentrated under vacuum. The solids were dissolved in 2ml hydrochloric acid (12 N) and again concentrated under vacuum. This resulted in 4.9 mg (21%) of (2R)-2-methyl-3-oxo-N-[(1R,3r,5S)-8-[(piperidin-4-ylmethane)sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide hydrochloride as a white solid. ¹HNMR (400 MHz, D₂O) δ : 7.32 (d, *J*= 8Hz, 1H), 7.21 (s, 1H), 7.01 (d, *J*= 8.4Hz, 1H), 4.79-4.72 (m, 1H), 4.21 (s, 2H), 4.04 (s, 1H), 3.37 (d, *J*= 12.8Hz, 2H), 3.20 (d, *J*= 6.4Hz, 2H), 2.95 (t, *J*= 10.4Hz, 2H), 2.25-2.15 (m, 3H), 2.14-2.00 (m, 6H), 1.95 (d, *J*= 14.8Hz, 2H), 1.65-1.40 (m, 5H) ppm. LCMS (method A, ESI): RT =1.49 min, *m/z* =477.3[M-HCl+H]⁺.

EXAMPLE 13

Synthesis of N-[(1R,3r,5S)-8-[4-(benzylamino)piperidine-1-sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-2-oxo-2,3-dihydro-1H-indole-5-carboxamide (Cpd. No. 587)

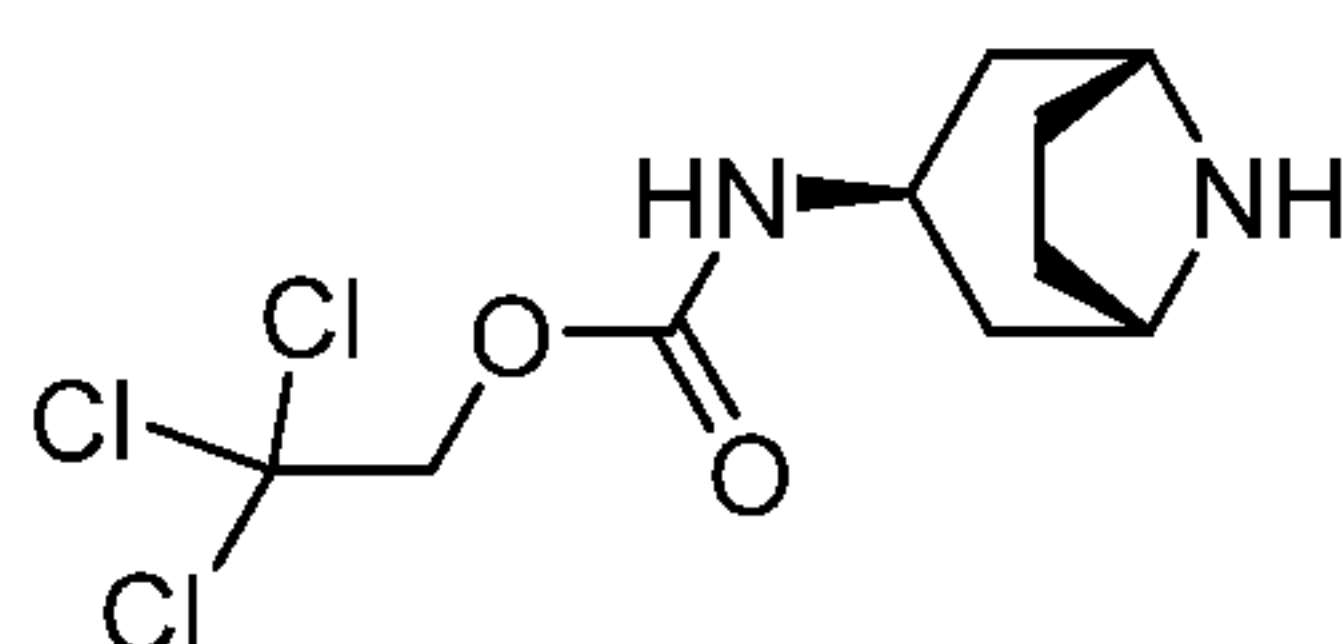


Step 1: Synthesis of tert-butyl (1R,3r,5S)-3-[[2,2,2-trichloroethoxy]carbonyl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate



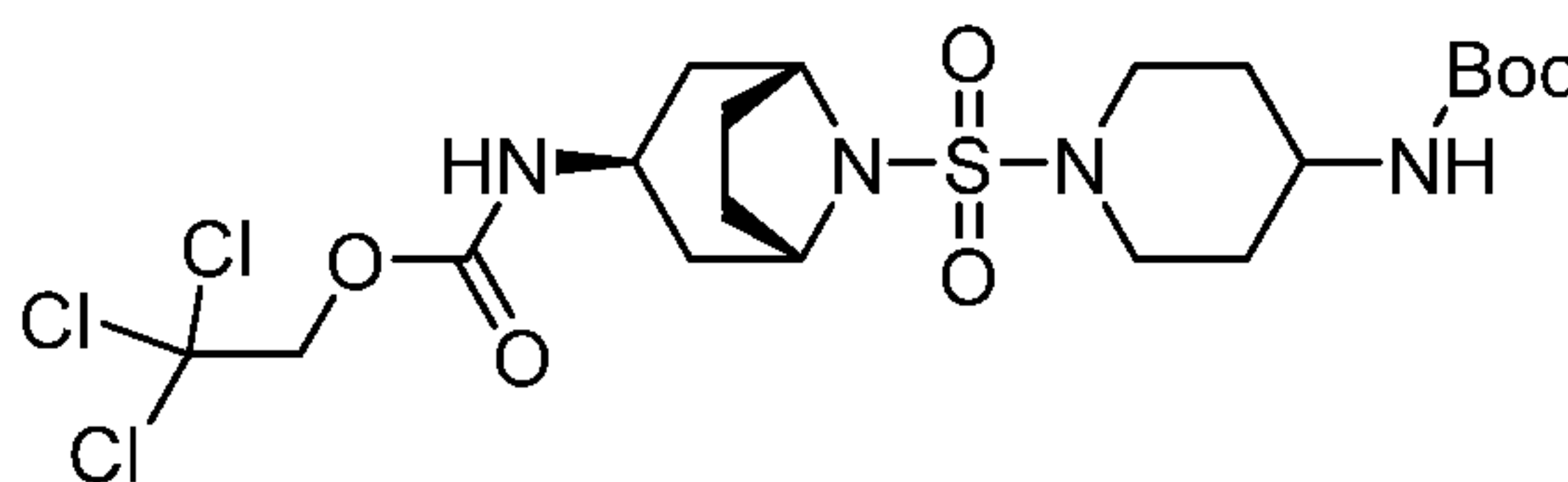
[0295] Into a 250-mL 3-necked round-bottom flask was placed tert-butyl (1R,3r,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (5 g, 22.09 mmol, 1.00 equiv), water (100 mL), and NaHCO₃ (4.83 g, 149.50 mmol, 2.60 equiv). The solution was cooled to 0°C and 2,2,2-trichloroethyl chloroformate (5.63 g, 26.57 mmol, 1.20 equiv) added dropwise over 10 mins. The resulting solution was stirred at room temperature overnight. The reaction mixture was extracted with 3x100 mL of dichloromethane and the organic layers combined. The combined extracts were washed with 3x100 mL of brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting residue was washed with 3x100 mL of hexane. This resulted in 8.32 g (94%) of tert-butyl (1R,3r,5S)-3-[[2,2,2-trichloroethoxy]carbonyl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate as a white solid. ¹H NMR (300 MHz, CDCl₃) δ : 5.30 (brs, 1H), 4.73 (s, 2H), 4.23 (brs, 2H), 4.00-3.89 (m, 1H), 2.30-2.17 (m, 2H), 2.12-2.03 (m, 2H), 1.90-1.80 (m, 2H), 1.78-1.69 (m, 2H), 1.46 (s, 9H) *ppm*. LCMS (method C, ESI): RT =1.27 min, *m/z* = 386.0 [M+H-15]⁺.

Step 2: Synthesis of 2,2,2-trichloroethyl N-[(1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl]carbamate



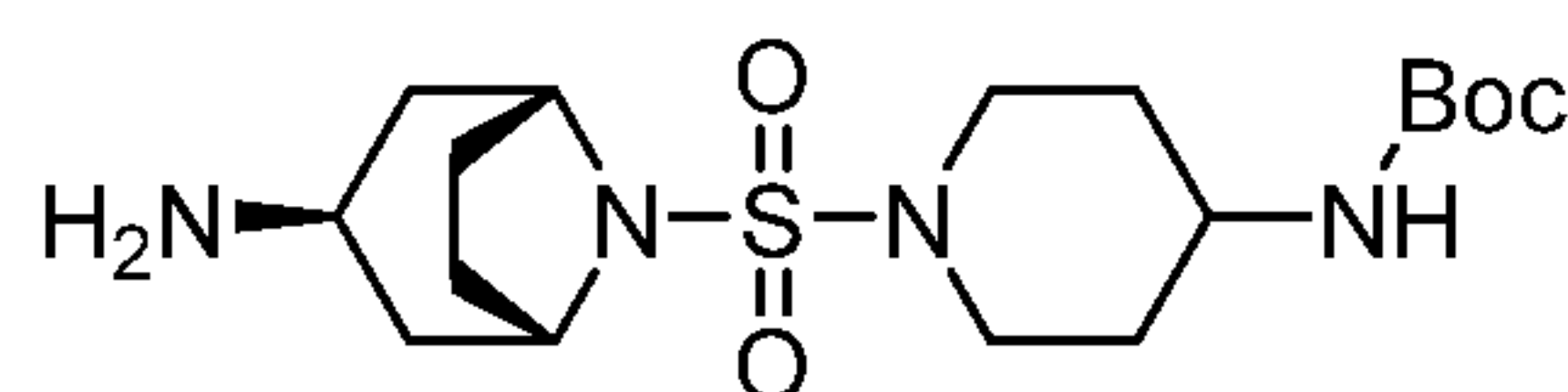
[0296] Into a 250-mL round-bottom flask was placed tert-butyl (1R,3r,5S)-3-[[2,2,2-trichloroethoxy]carbonyl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (4 g, 9.96 mmol, 1.00 equiv) and dichloromethane (40 mL). To this hydrogen chloride (gas) was introduced. The resulting solution was stirred for 1 h at room temperature. The mixture was then concentrated under vacuum. This resulted in 3.3 g (98%) of 2,2,2-trichloroethyl N-[(1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl]carbamate hydrochloride as a white solid. ¹H NMR (300 MHz, D₂O) δ : 4.72 (s, 2H), 4.09 (brs, 2H), 3.83-3.75(m, 1H), 2.28-1.95 (m, 8H) *ppm*.

Step 3: Synthesis of 2,2,2-trichloroethyl N-[(1R,3r,5S)-8-(4-[[[(tert-butoxy)carbonyl]amino]piperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]carbamate



[0297] Into a 25-mL round-bottom flask was placed 2,2,2-trichloroethyl N-[(1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl]carbamate hydrochloride (1.0 g, 2.96 mmol, 1.00 equiv) and dichloromethane (15 mL). This was followed by the addition of TEA (1.5 g, 14.82 mmol, 5.01 equiv) dropwise with stirring at 0°C. To this was then added tert-butyl N-[1-(chlorosulfonyl)piperidin-4-yl]carbamate (1.8 g, 6.02 mmol, 2.04 equiv) in several batches at 0°C. The resulting solution was stirred for 14 h at 20 °C. The reaction mixture was diluted with 35 mL of dichloromethane and washed with 3x10 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (1:2). This resulted in 1.5 g (90%) of 2,2,2-trichloroethyl N-[(1R,3r,5S)-8-(4-[[[(tert-butoxy)carbonyl]amino]piperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]carbamate as a white solid. ¹H NMR (400 MHz, CDCl₃) δ : 5.22 (brs, 1H), 4.75 (s, 2H), 4.46 (brs, 1H), 4.13 (brs, 2H), 4.01-3.95 (m, 1H), 3.70 (d, *J*=12.0Hz, 2H), 3.58 (brs, 1H), 2.84 (t, *J*=11.2Hz, 2H), 2.33-2.14 (m, 4H), 2.10-1.98 (m, 2H), 1.96-1.84 (m, 3H), 1.65-1.50 (m, 3H), 1.47 (s, 9H) *ppm*. LCMS (method D, ESI): RT =1.58 min, *m/z* = 507.0 [M+H-56]⁺.

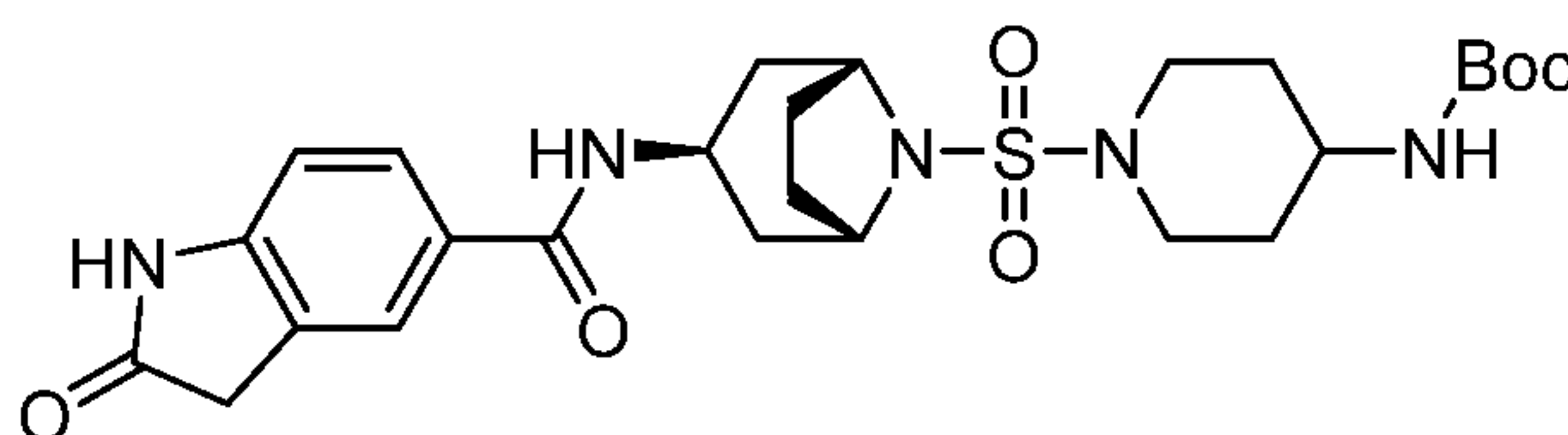
Step 4: Synthesis of tert-butyl N-[1-[(1R,3r,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate



[0298] Into a 100-mL round-bottom flask was placed 2,2,2-trichloroethyl N-[(1R,3r,5S)-8-(4-[[[(tert-butoxy)carbonyl]amino]piperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]carbamate (1.0 g, 1.77 mmol, 1.00 equiv), AcOH (15 mL), zinc (1.73 g, 26.45 mmol, 14.92 equiv) and water(1 mL). The resulting mixture was stirred for 1 h at 25°C. The mixture was then diluted with 30 mL of H₂O and the solids were filtered out. The pH was adjusted to 9 with sodium carbonate (aq. sat.). The resulting solution was extracted with 5x30 mL of dichloromethane and the organic layers combined. After concentration this resulted in 500 mg (73%) of tert-butyl N-[1-[(1R,3r,5S)-3-amino-8-

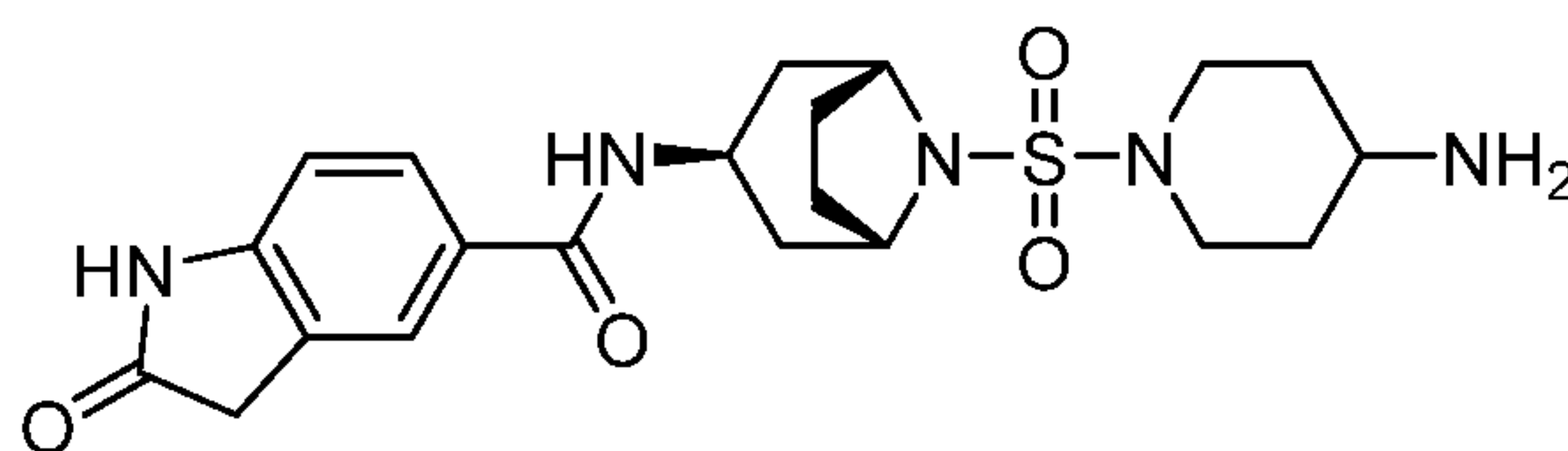
azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate as a white solid. LCMS (method A, ESI): RT = 1.08 min, m/z = 333.0 $[M+H-56]^+$.

Step 5: Synthesis of tert-butyl N-[1-[(1R,3r,5S)-3-(2-oxo-2,3-dihydro-1H-indole-5-carboxamido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate



[0299] Into a 25-mL round-bottom flask was placed tert-butyl N-[1-[(1R,3r,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate (200 mg, 0.51 mmol, 1.00 equiv), dichloromethane (5 mL), 2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid (109 mg, 0.62 mmol, 1.20 equiv), EDCI (118 mg, 0.62 mmol, 1.20 equiv), and HOBT (104 mg, 0.77 mmol, 1.50 equiv). This was followed by the addition of TEA (260 mg, 2.57 mmol, 4.99 equiv) dropwise with stirring at 0°C. The resulting solution was stirred for 14 h at 20°C. The reaction mixture was then diluted with 10 mL of dichloromethane and was washed with 2x5 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 243 mg (86%) of tert-butyl N-[1-[(1R,3r,5S)-3-(2-oxo-2,3-dihydro-1H-indole-5-carboxamido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate as a off-white solid. LCMS (method A, ESI): RT = 1.27 min, m/z = 448.0 $[M+H-100]^+$.

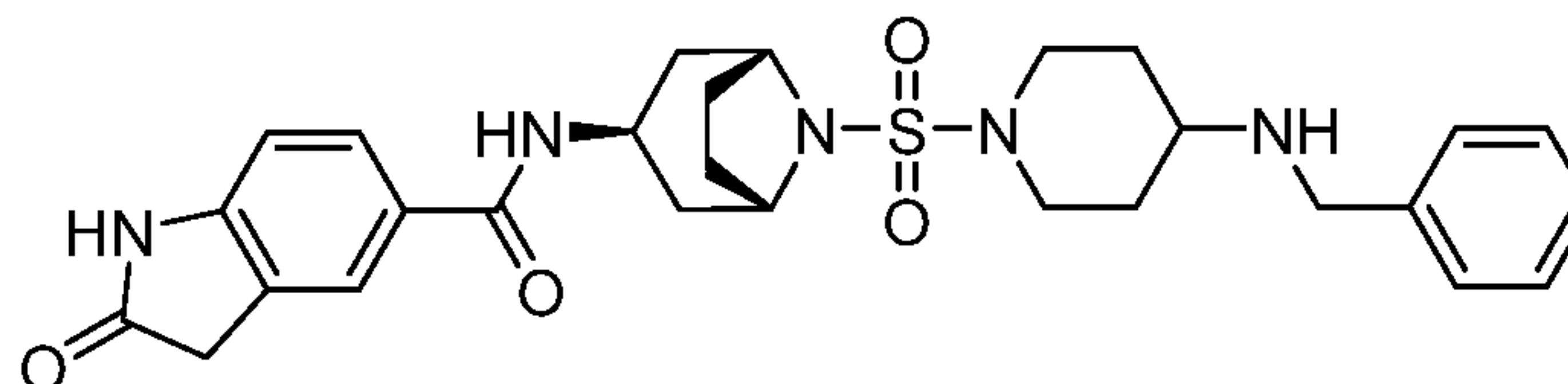
Step 6: Synthesis of N-[(1R,3r,5S)-8-(4-aminopiperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-2-oxo-2,3-dihydro-1H-indole-5-carboxamide



[0300] Into a 25-mL round-bottom flask was placed tert-butyl N-[1-[(1R,3r,5S)-3-(2-oxo-2,3-dihydro-1H-indole-5-carboxamido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate (241 mg, 0.44 mmol, 1.00 equiv) and dichloromethane (5 mL). To this hydrogen chloride (gas) was introduced. The resulting solution was stirred for 2 h at 15°C. The mixture was then concentrated under vacuum. This resulted in 200 mg (94%) of N-[(1R,3r,5S)-8-(4-aminopiperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-2-oxo-2,3-dihydro-1H-indole-5-carboxamide hydrochloride

as a yellow solid. ^1H NMR (400 MHz, CD_3OD) : 7.70 (d, $J=8.0\text{Hz}$, 2H), 6.97 (d, $J=8.0\text{Hz}$, 1H), 4.14 (s, 3H), 3.86 (d, $J=13.2\text{Hz}$, 2H), 3.61 (s, 2H), 3.31-3.25 (m, 1H), 2.91 (t, $J=12.4\text{Hz}$, 2H), 2.37-2.25 (m, 2H), 2.21-1.98 (m, 8H), 1.76-1.63 (m, 2H) ppm. LCMS (method A, ESI): RT = 1.07 min, m/z = 448.3 $[\text{M}+\text{H}]^+$.

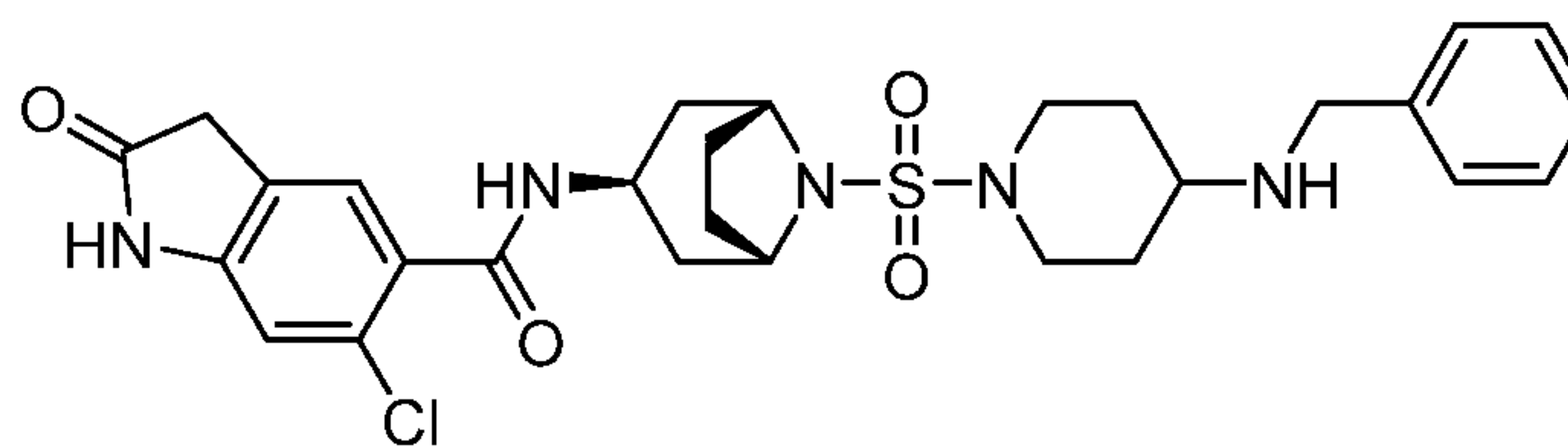
Step 7: Synthesis of N-[(1R,3r,5S)-8-[4-(benzylamino)piperidine-1-sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-2-oxo-2,3-dihydro-1H-indole-5-carboxamide



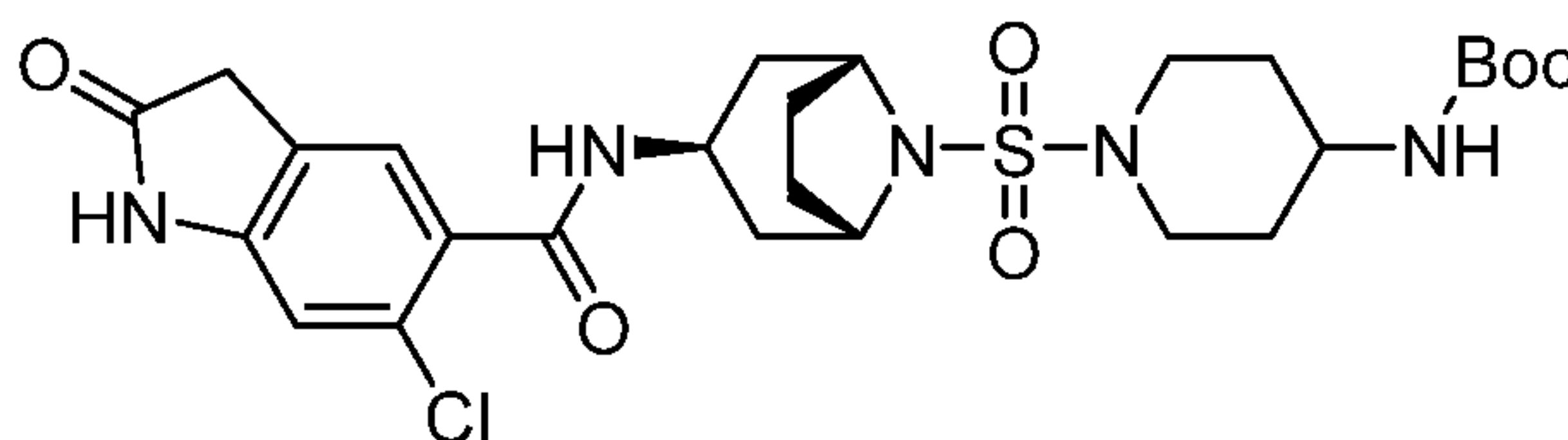
[0301] Into a 25-mL round-bottom flask was placed N-[(1R,3r,5S)-8-(4-aminopiperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-2-oxo-2,3-dihydro-1H-indole-5-carboxamide hydrochloride (60 mg, 0.12 mmol, 1.00 equiv), methanol (5 mL), and benzaldehyde (13 mg, 0.12 mmol, 0.99 equiv). The mixture was stirred for 0.5 h at 20°C. To this NaBH_3CN (7.8 mg, 0.12 mmol, 1.00 equiv) was added in batches. The resulting solution was stirred for 2 h at 70°C. The reaction mixture was concentrated under vacuum. The residue was diluted with 5 mL of H_2O and extracted with 2x5 mL of dichloromethane. The organic layers combined and concentrated. The crude product was purified by Prep-HPLC with the following conditions: Column, X Bridge C18, 19*150 mm, 5 μm ; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 30%B to 70%B in 10 min; Detector, 254nm. This resulted in 14.8 mg (18%) of N-[(1R,3r,5S)-8-[4-(benzylamino)piperidine-1-sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-2-oxo-2,3-dihydro-1H-indole-5-carboxamide trifluoroacetic acid as a white solid. ^1H NMR (300 MHz, CD_3OD) : 7.70 (d, $J=7.8\text{Hz}$, 2H), 7.69-7.48 (m, 5H), 6.97 (d, $J=8.4\text{Hz}$, 1H), 4.28 (s, 2H), 4.14 (s, 3H), 3.92 (d, $J=12.6\text{Hz}$, 2H), 3.60 (s, 2H), 3.54-3.35 (m, 1H), 2.90 (t, $J=13.2\text{Hz}$, 2H), 2.35-2.22 (m, 4H), 2.21-2.10 (m, 4H), 2.09-1.98 (m, 2H), 1.85-1.68 (m, 2H) ppm. LCMS (method A, ESI): RT = 2.26 min, m/z = 538.4 $[\text{M}+\text{H}]^+$.

EXAMPLE 14

Synthesis of N-[(1R,3r,5S)-8-[4-(benzylamino)piperidine-1-sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-6-chloro-2-oxo-2,3-dihydro-1H-indole-5-carboxamide trifluoroacetate (Cpd. No. 592)

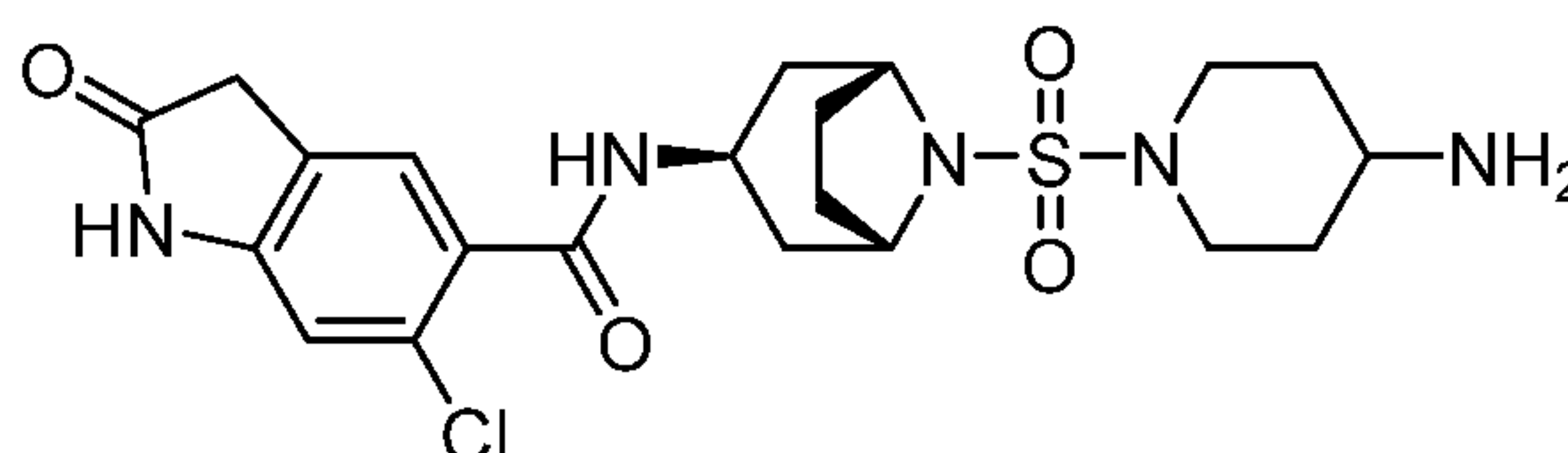


Step 1: Synthesis of tert-butyl N-[1-[(1R,3r,5S)-3-(6-chloro-2-oxo-2,3-dihydro-1H-indole-5-carboxamido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate



[0302] Into a 25-mL round-bottom flask was placed 6-chloro-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid (170 mg, 0.80 mmol, 1.00 equiv), dichloromethane (10 mL), HOBT (216 mg, 1.60 mmol, 2.00 equiv), EDCI (306 mg, 1.60 mmol, 2.00 equiv), and tert-butyl N-1-[(1R,3r,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-ylcarbamate (375 mg, 0.97 mmol, 1.20 equiv). This was followed by the addition of TEA (400 mg, 3.95 mmol, 5.00 equiv) dropwise with stirring at 0°C. The resulting solution was stirred for 2 h at room temperature. The reaction mixture was diluted with 10 mL of dichloromethane and washed with 2x5 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (3:1). This resulted in 300 mg (64%) of tert-butyl N-[1-[(1R,3r,5S)-3-(6-chloro-2-oxo-2,3-dihydro-1H-indole-5-carboxamido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate as a red solid. LCMS (method C, ESI): RT = 0.88 min, m/z = 582.0 $[M+H]^+$.

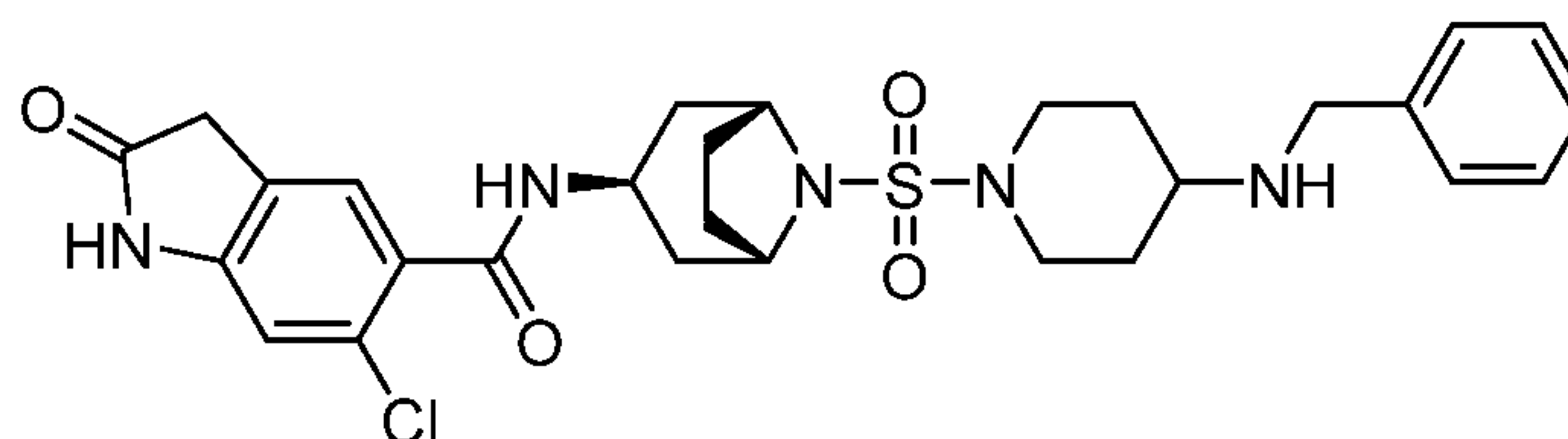
Step 2: Synthesis of N-[(1R,3r,5S)-8-(4-aminopiperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-6-chloro-2-oxo-2,3-dihydro-1H-indole-5-carboxamide hydrochloride



[0303] Into a 25-mL round-bottom flask was placed tert-butyl N-[1-[(1R,3r,5S)-3-(6-chloro-2-oxo-2,3-dihydro-1H-indole-5-carboxamido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate (300 mg, 0.52 mmol, 1.00 equiv) and hydrogen

chloride/dioxane (10 mL, saturated, this solution was made by introducing hydrogen chloride gas into 1,4-dioxane under 0°C for 6 hours). The resulting solution was stirred for 4 h at room temperature. The mixture was then concentrated under vacuum. This resulted in 170 mg (64%) of N-[(1R,3r,5S)-8-(4-aminopiperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-6-chloro-2-oxo-2,3-dihydro-1H-indole-5-carboxamide hydrochloride as a red solid. LCMS (method A, ESI): RT =0.96 min, m/z = 482.0 $[M+H]^+$.

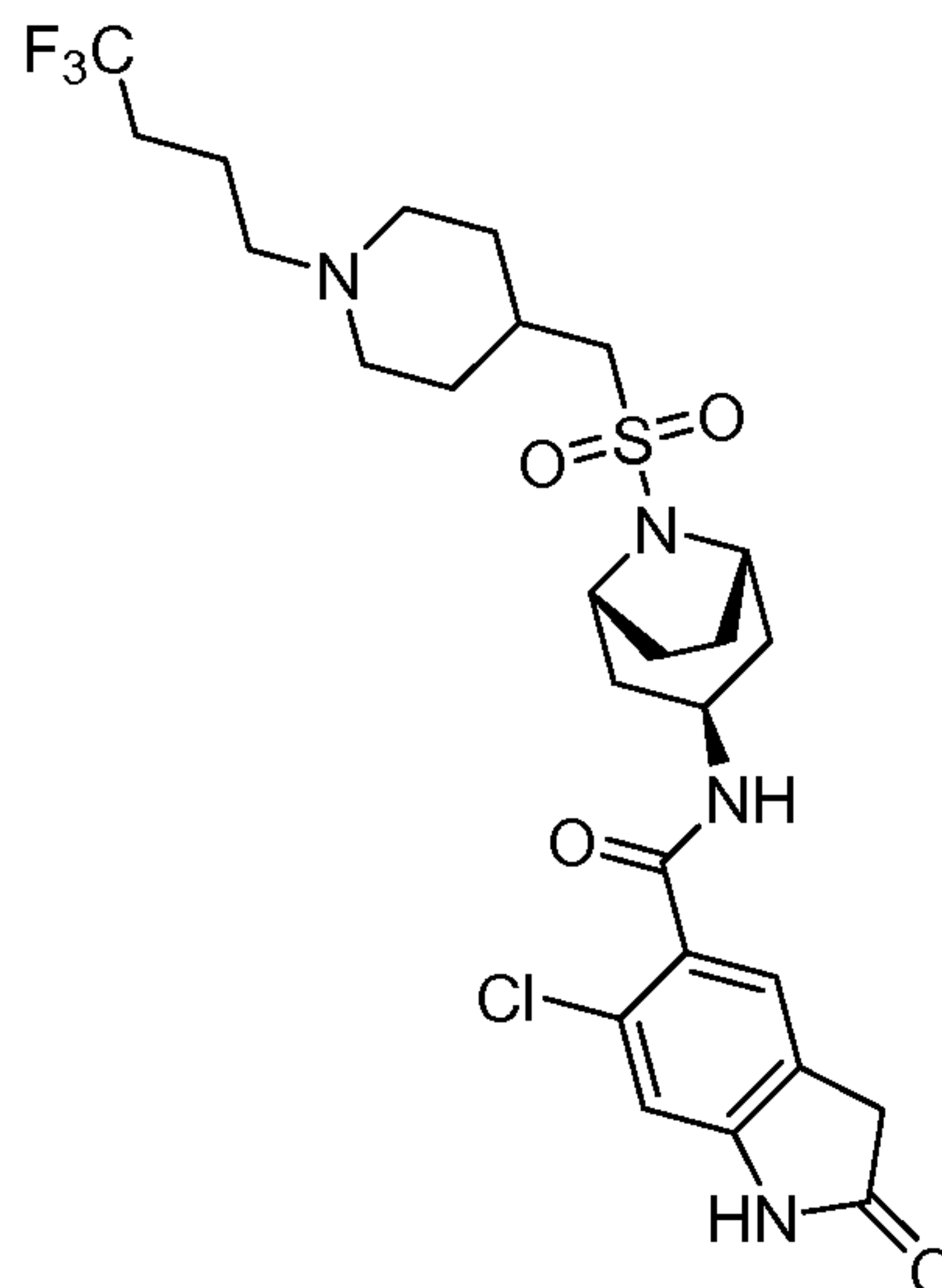
Step 3: Synthesis of N-[(1R,3r,5S)-8-[4-(benzylamino)piperidine-1-sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-6-chloro-2-oxo-2,3-dihydro-1H-indole-5-carboxamide; trifluoroacetic acid



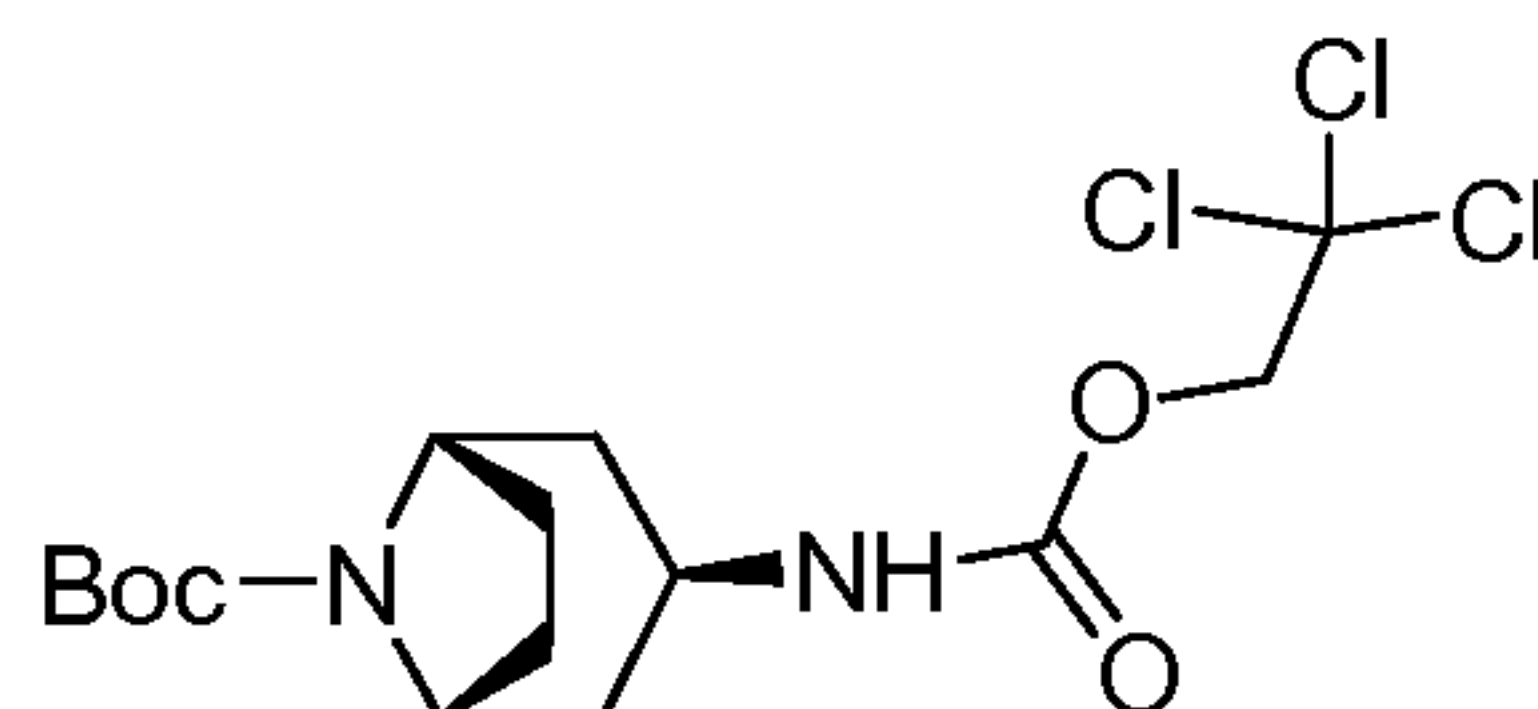
[0304] Into a 25-mL round-bottom flask was placed N-[(1R,3r,5S)-8-(4-aminopiperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-6-chloro-2-oxo-2,3-dihydro-1H-indole-5-carboxamide hydrochloride (50 mg, 0.10 mmol, 1.00 equiv), methanol (5 mL), and benzaldehyde (12.3 mg, 0.12 mmol, 1.20 equiv). The mixture was stirred for 0.5 h at 20 °C. To the above NaBH_3CN (7.3 mg, 0.12 mmol, 1.20 equiv) was added in batches. The resulting solution was stirred for 1 h at 70°C. The reaction mixture was then concentrated under vacuum and the crude product purified by Prep-HPLC with the following conditions: Column: X Select C18, 19*250 mm, 5 μm ; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 5%B to 36%B in 12.5 min; Detector: 254nm. This resulted in 28 mg (42%) of N-[(1R,3r,5S)-8-[4-(benzylamino)piperidine-1-sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-6-chloro-2-oxo-2,3-dihydro-1H-indole-5-carboxamide trifluoroacetate as a white solid. ^1H NMR (400 MHz, CD_3OD) : 7.53-7.49 (m, 5H), 7.33 (s, 1H), 6.97 (s, 1H), 4.29 (s, 2H), 4.16 (s, 3H), 3.91 (d, $J=12.8\text{Hz}$, 2H), 3.57 (s, 2H), 3.41-3.37 (m, 1H), 2.89 (t, $J=10.8\text{Hz}$, 2H), 2.37-2.21 (m, 4H), 2.20-2.08 (m, 4H), 2.05-1.96 (m, 2H), 1.80-1.70 (m, 2H) ppm. LCMS (method A, ESI): RT =1.31 min, m/z = 572.2 $[M+H]^+$.

EXAMPLE 15

Synthesis of 6-chloro-2-oxo-N-((1S,3r,5R)-8-((1-(4,4,4-trifluorobutyl)piperidin-4-yl)methylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)indoline-5-carboxamide
(Cpd. No. 595)

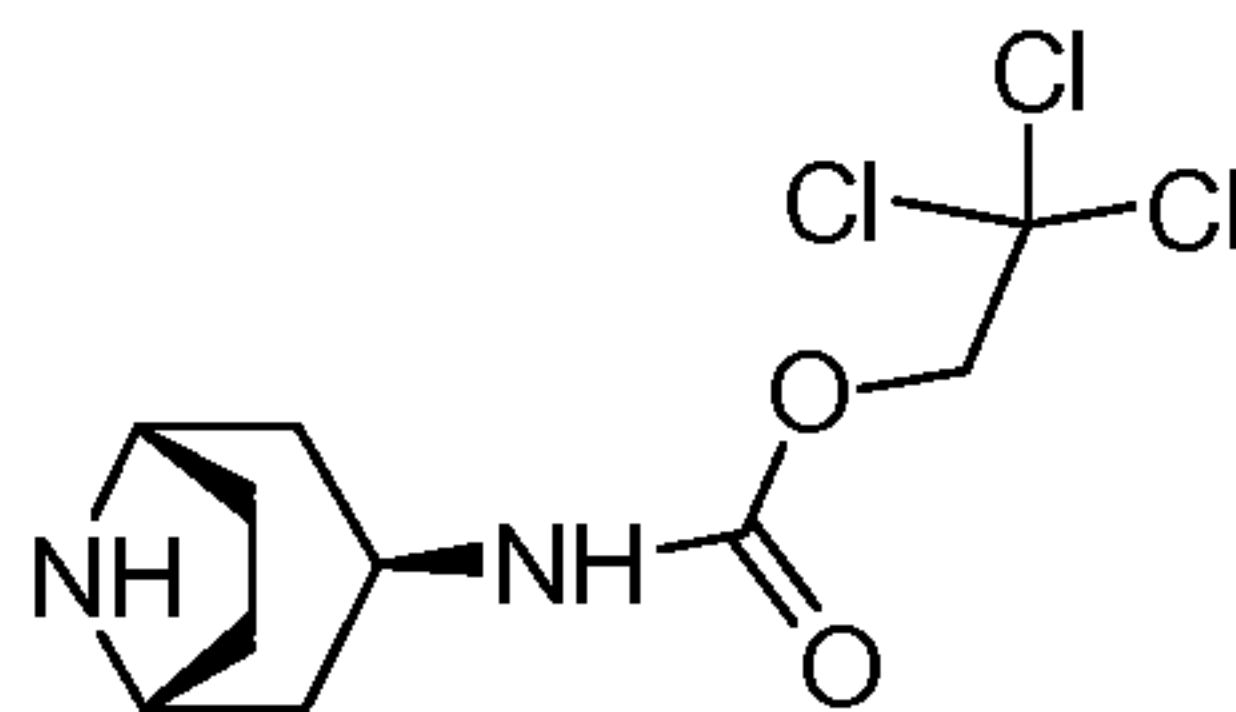


Step 1: Synthesis of tert-butyl (1R,3S,5S)-3-[[2,2,2-trichloroethoxy]carbonyl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate



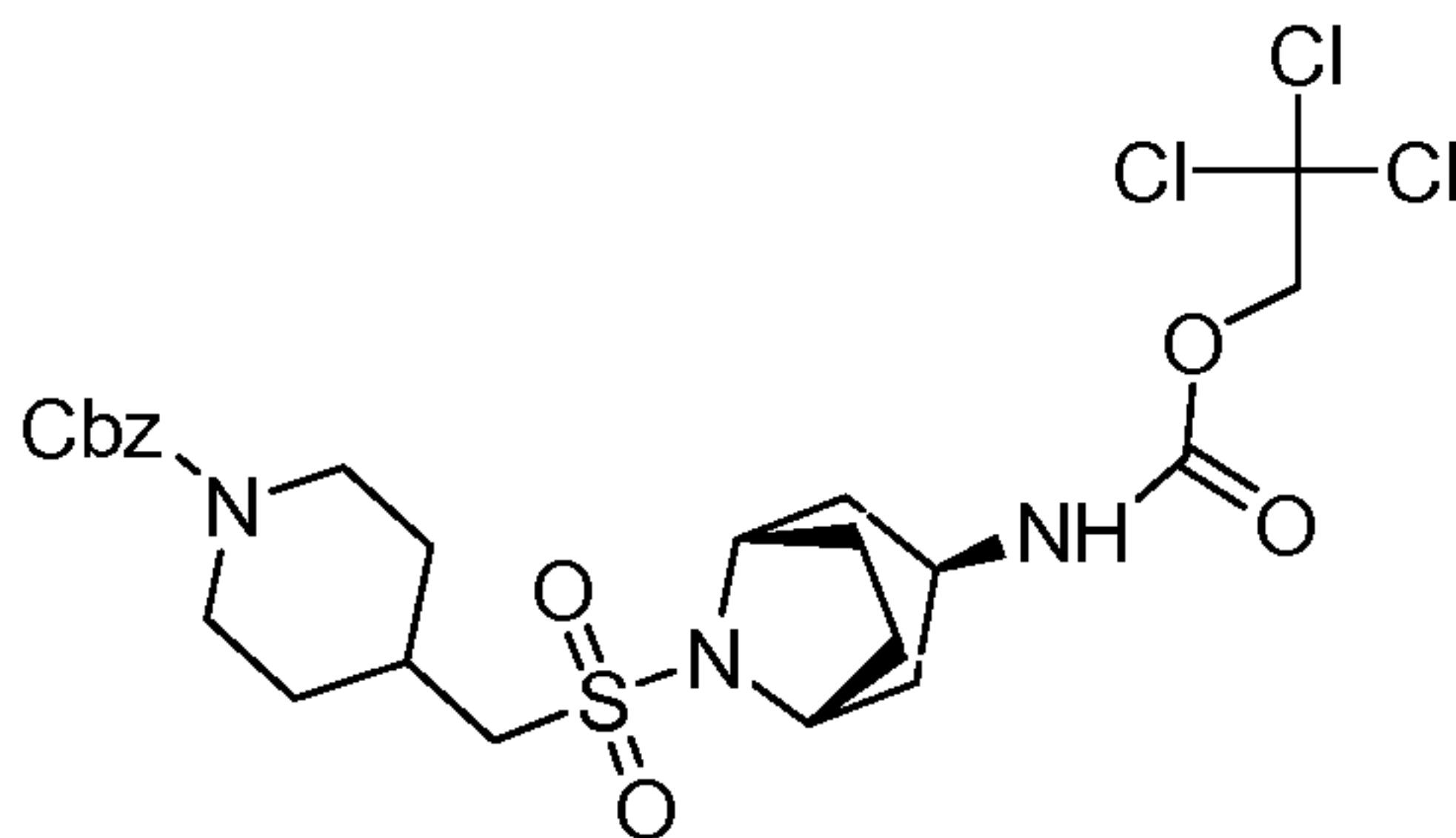
[0305] Into a 250-mL round-bottom flask, was placed water (120 mL). This was followed by the addition of tert-butyl (1R,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (2 g, 8.84 mmol, 1.00 equiv), sodium bicarbonate (1.92 g, 22.85 mmol, 2.59 equiv). To the mixture was added 2,2,2-trichloroethyl chloroformate (2.28 g, 10.76 mmol, 1.22 equiv) dropwise with stirring at 0°C. The resulting solution was stirred for 18 h at 20°C. The resulting solution was extracted with 3x150 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 4.16 g (crude) of tert-butyl (1R,5S)-3-[[2,2,2-trichloroethoxy]carbonyl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate as a white solid. ¹H NMR(300 MHz, CDCl₃): δ 4.75(s, 2H), 4.25 (s, 2H), 4.00-3.90(m, 1H), 2.29-2.00(m, 4H), 2.89-2.71(m, 4H), 1.45(s, 9H) ppm.

Step 2: Synthesis of 2,2,2-trichloroethyl (1S,3r,5R)-8-aza-bicyclo[3.2.1]octan-3-ylcarbamate



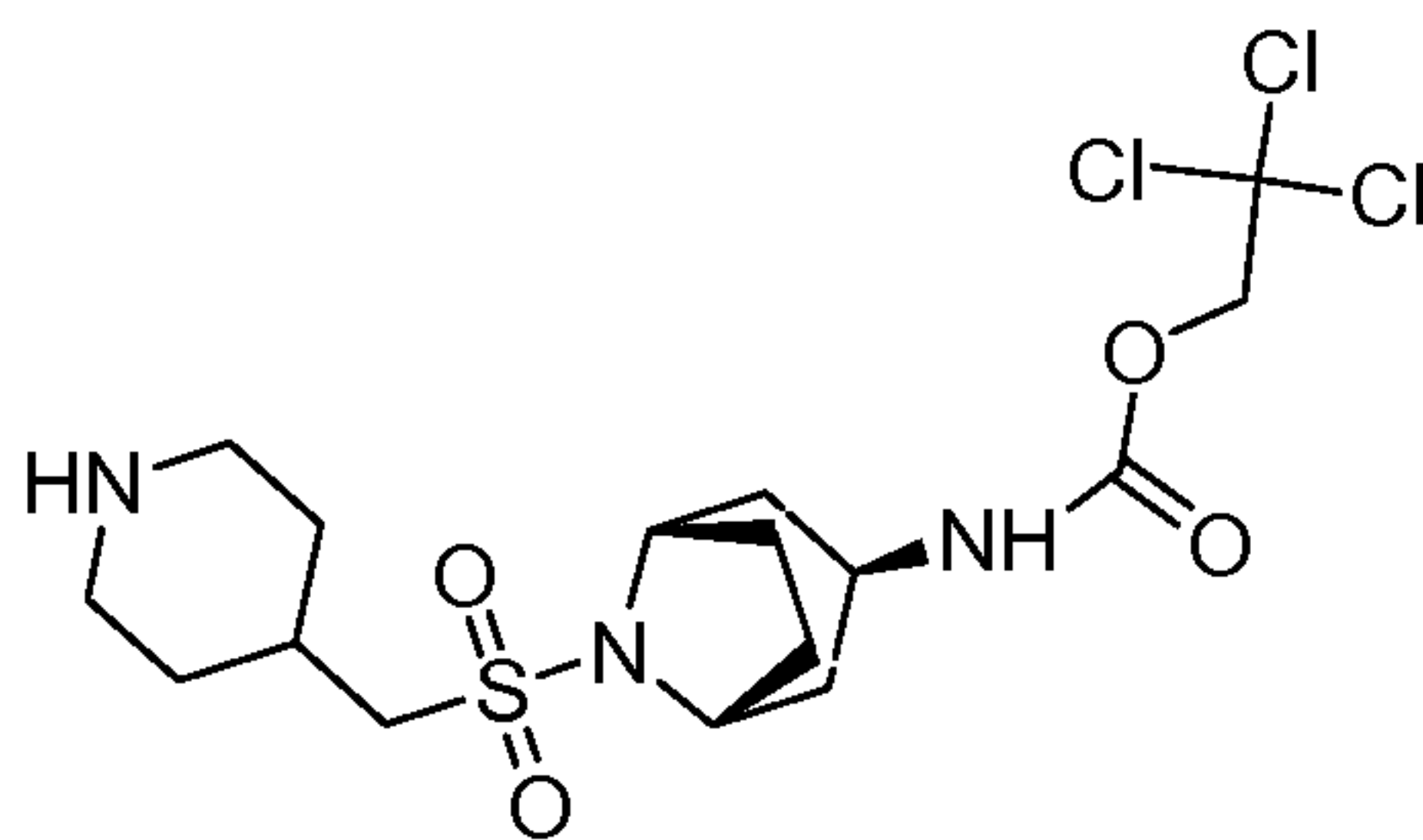
[0306] Into a 100-mL round-bottom flask, was placed dichloromethane (20 mL), tert-butyl ((1R,3S,5S)-3-(((2,2,2-trichloroethoxy)carbonyl)amino)-8-azabicyclo[3.2.1]octan-8-carboxylate (2 g, 4.98 mmol, 1.00 equiv). Then hydrogen chloride gas was introduced into mixture. The resulting solution was stirred for 12 h at 80°C. The resulting mixture was concentrated under vacuum. This resulted in 1.7 g (crude) of 2,2,2-trichloroethyl N-[(1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl]carbamate as a yellow solid. LCMS (method D, ESI): RT = 0.86 min, m/z = 303.2 $[M+H]^+$.

Step 3: Synthesis of benzyl 4-(((1S,3r,5R)-3-(((2,2,2-trichloroethoxy)carbonylamino)-8-aza-bicyclo[3.2.1]octan-8-ylsulfonyl)methyl)piperidine-1-carboxylate



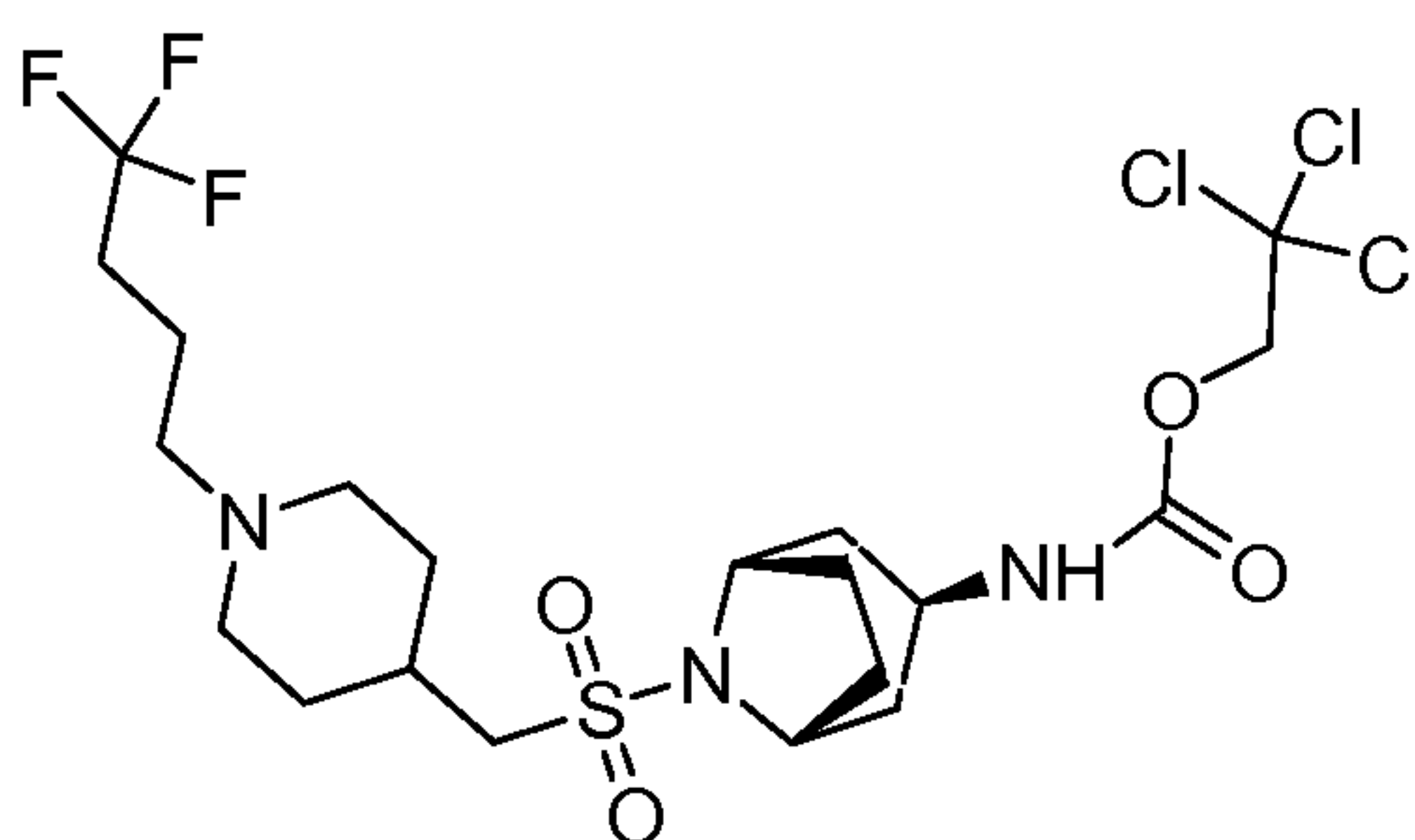
[0307] Into a 100-mL round-bottom flask, was placed dichloromethane (30 mL), 2,2,2-trichloroethyl N-[(1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl]carbamate (2.4 g, 7.96 mmol, 1.00 equiv), TEA (3.2 g, 31.62 mmol, 3.97 equiv). Then benzyl 4-[(chlorosulfonyl)methyl]piperidine-1-carboxylate (4 g, 12.05 mmol, 1.51 equiv) was added by dropwise at 0°C. The resulting solution was stirred for 12 h at 10°C. The resulting mixture was washed with 3x30 mL of water and 1x30 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (20:1). This resulted in 2.8 g (59%) of benzyl 4-[(1R,3S,5S)-3-(((2,2,2-trichloroethoxy)carbonyl)amino)-8-azabicyclo[3.2.1]octane-8-sulfonyl]methyl]piperidine-1-carboxylate as a yellow solid. ^1H NMR(300 MHz, CDCl_3): δ 7.41-7.30 (m, 5H), 5.15 (s, 2H), 4.75 (s, 2H), 4.30-4.15(m, 4H), 4.05-3.90 (m, 1H), 2.95-2.76 (m, 4H), 2.35-2.10 (m, 4H), 2.10-1.90 (m, 5H), 1.57(s, 1H), 1.40-1.20(m, 3H) ppm. LCMS (method D, ESI): RT = 1.15 min, m/z = 596.1 $[M+H]^+$.

Step 4 2,2,2-trichloroethyl (1S,3r,5R)-8-(piperidin-4-ylmethylsulfonyl)-8-azabicyclo[3.2.1]octan-3-ylcarbamate hydrochloride salts



[0308] Into a 250-mL round-bottom flask, was placed benzyl 4-[[[(1R,5S)-3-[[[(2,2,2-trichloroethoxy)carbonyl]amino]-8-azabicyclo[3.2.1]octane-8-sulfonyl]methyl]piperidine-1-carboxylate (1.5 g, 2.51 mmol, 1.00 equiv). This was followed by the addition of hydrochloric acid (12 N, 140 mL) at 10°C. The resulting solution was stirred for 12 h at 50°C. The resulting mixture was concentrated under vacuum. This resulted in 1.1 g (88%) of 2,2,2-trichloroethyl N-[(1R,5S)-8-[(piperidin-4-ylmethane)sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]carbamate hydrochloride as a yellow solid. LCMS (method D, ESI): RT = 0.67 min, m/z = 464.0 $[M+H]^+$.

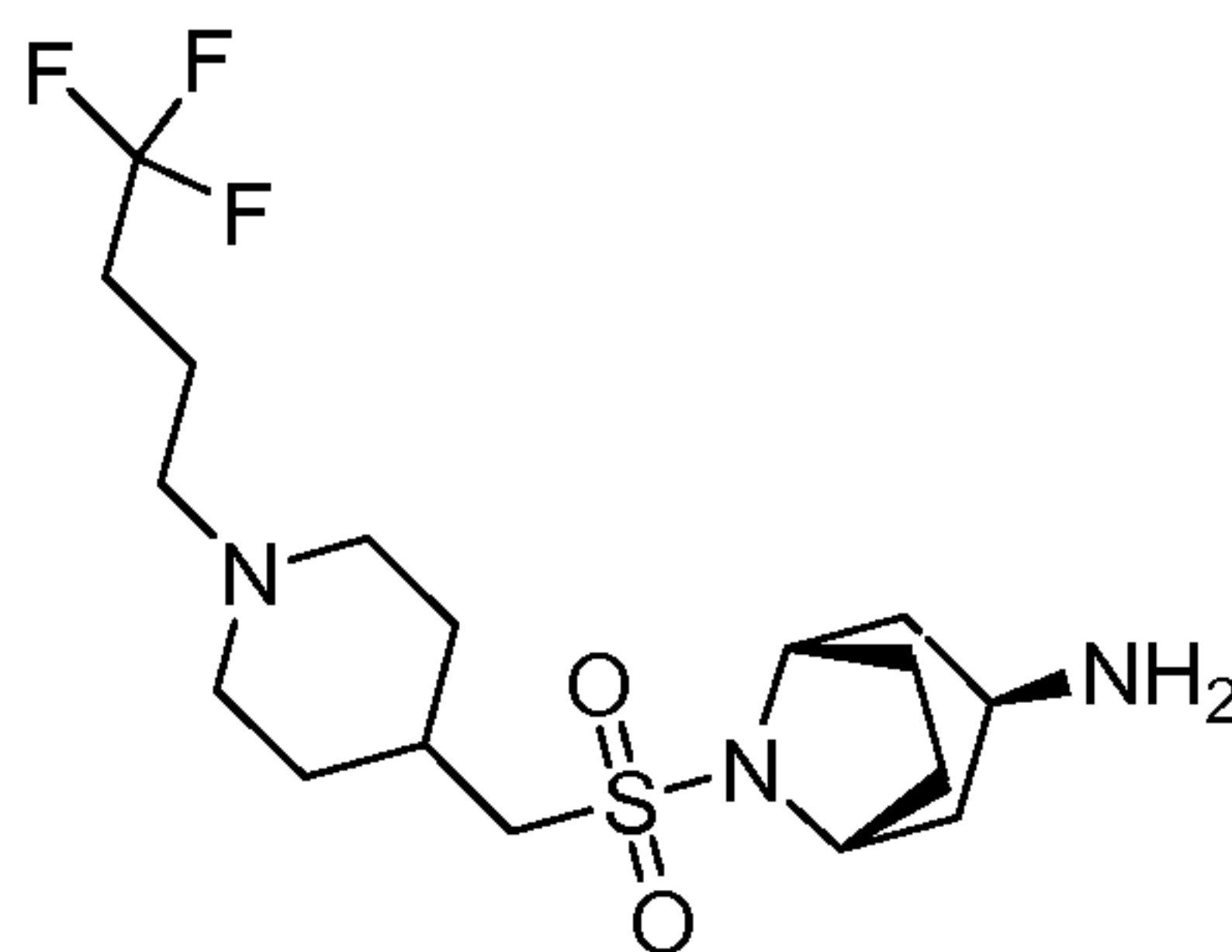
Step 5: Synthesis of 2,2,2-trichloroethyl (1S,3r,5R)-8-((1-(4,4,4-trifluorobutyl)piperidin-4-yl)methylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-ylcarbamate



[0309] Into a 100-mL round-bottom flask, was placed dichloromethane (40 mL). This was followed by the addition of methanol (20 mL), 2,2,2-trichloroethyl N-[(1R,5S)-8-[(piperidin-4-ylmethane)sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]carbamate hydrochloride (300 mg, 0.60 mmol, 1.00 equiv), 4,4,4-trifluorobutanal (227 mg, 1.80 mmol, 3.00 equiv). Then NaBH₃CN (303 mg, 4.81 mmol, 8.00 equiv) was added into by batchwise. To the mixture was added acetic acid (1 mL). The resulting solution was stirred for 6 h at 10°C. The resulting mixture was concentrated under vacuum. The resulting solution was extracted with 3x100 mL of dichloromethane and the organic layers combined. The resulting mixture was washed with 1x50 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue

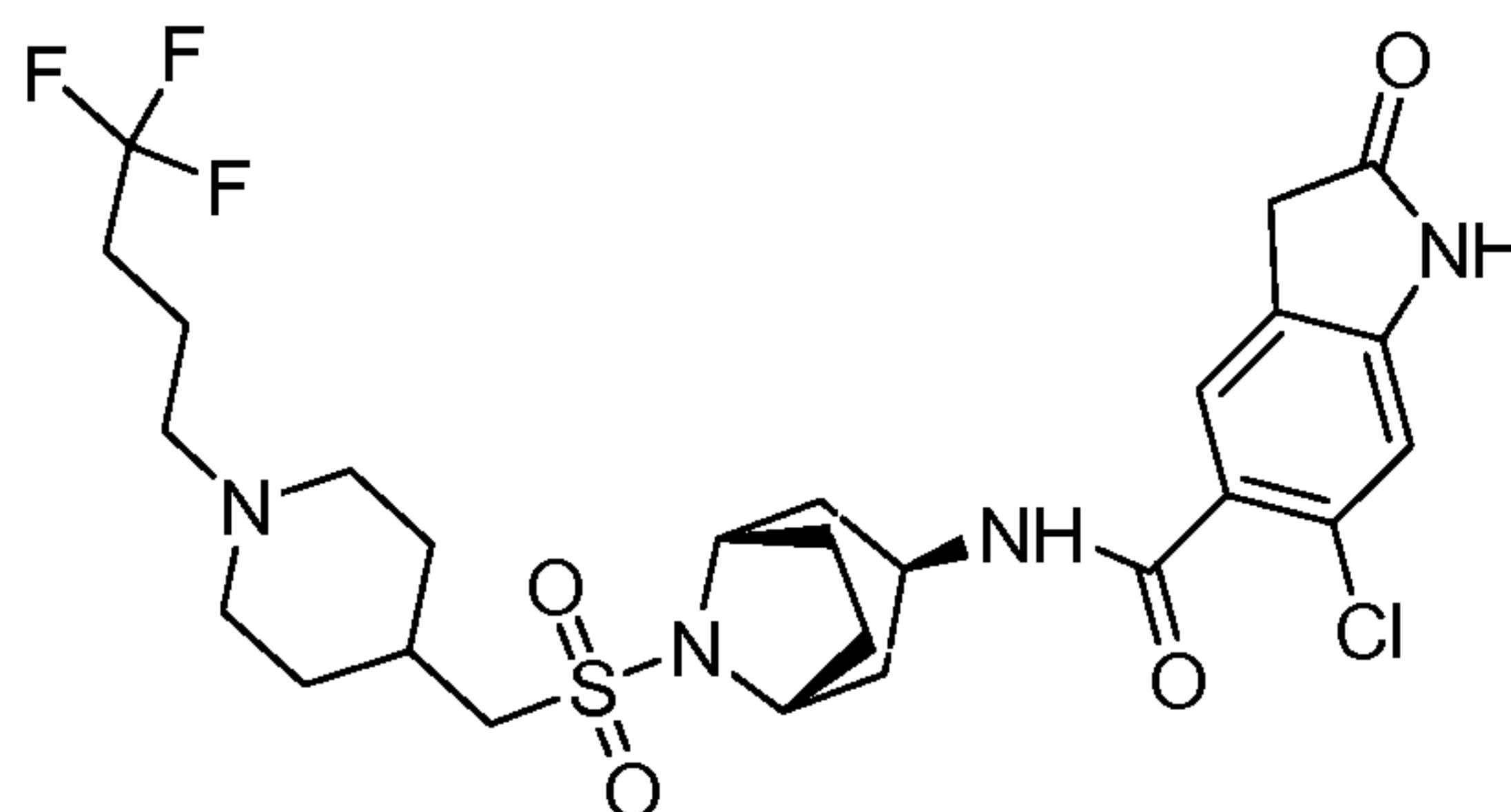
was purified by flash chromatography with eluent (PE/EtOAc=2/1 to 100% EtOAc). This resulted in 295 mg (86%) of 2,2,2-trichloroethyl N-[(1R,5S)-8-([1-(4,4,4-trifluorobutyl)piperidin-4-yl]methane)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]carbamate as yellow oil. ^1H NMR(300 MHz, CDCl_3): δ 4.75 (s, 2H), 4.30 (s, 2H), 4.02-3.95 (m, 1H), 3.10-3.02 (m, 2H), 3.00-2.95 (m, 2H), 2.58-2.50 (m, 2H), 2.32-1.78 (m, 17H), 1.60-1.48 (m, 2H) ppm. LCMS (method D, ESI): RT = 0.97 min, m/z = 572.0 $[\text{M}+\text{H}]^+$.

Step 6: Synthesis of (1S,3r,5R)-8-((1-(4,4,4-trifluorobutyl)piperidin-4-yl)methylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-amine



[0310] Into a 100-mL round-bottom flask, was placed 2,2,2-trichloroethyl N-[(1R,3S,5S)-8-([1-(4,4,4-trifluorobutyl)piperidin-4-yl]methane)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]carbamate (50 mg, 0.09 mmol, 1.00 equiv). This was followed by the addition of acetic acid (15 mL), water (1 mL) and Zn (90 mg). The resulting solution was stirred for 12 h at 10°C. The solids were filtered out. The pH value of the solution was adjusted to 8 with sodium carbonate (sat. aq.). The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. This resulted in 25 mg (72%) of (1R,3S,5S)-8-([1-(4,4,4-trifluorobutyl)piperidin-4-yl]methane)sulfonyl)-8-azabicyclo[3.2.1]octan-3-amine as a yellow solid. LCMS (method B, ESI): RT = 1.24 min, m/z = 398.0 $[\text{M}+\text{H}]^+$.

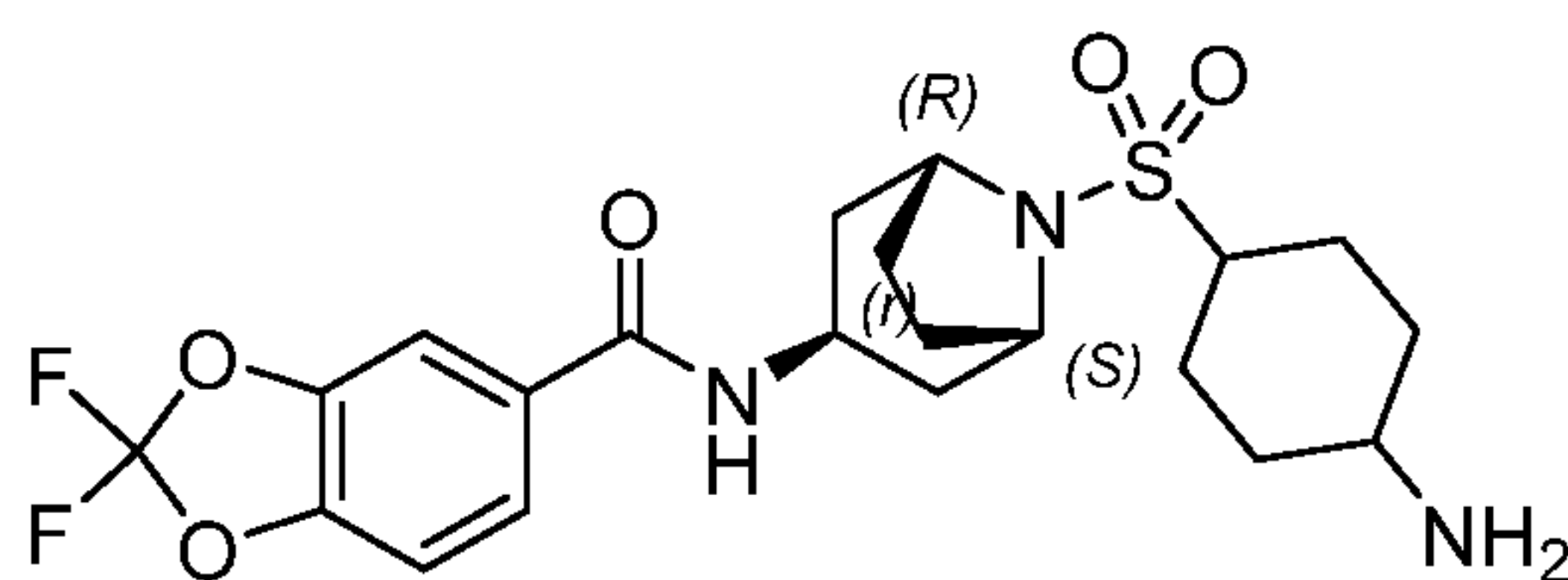
Step 7: Synthesis of 6-chloro-2-oxo-N-((1S,3r,5R)-8-((1-(4,4,4-trifluorobutyl)piperidin-4-yl)methylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)indoline-5-carboxamide



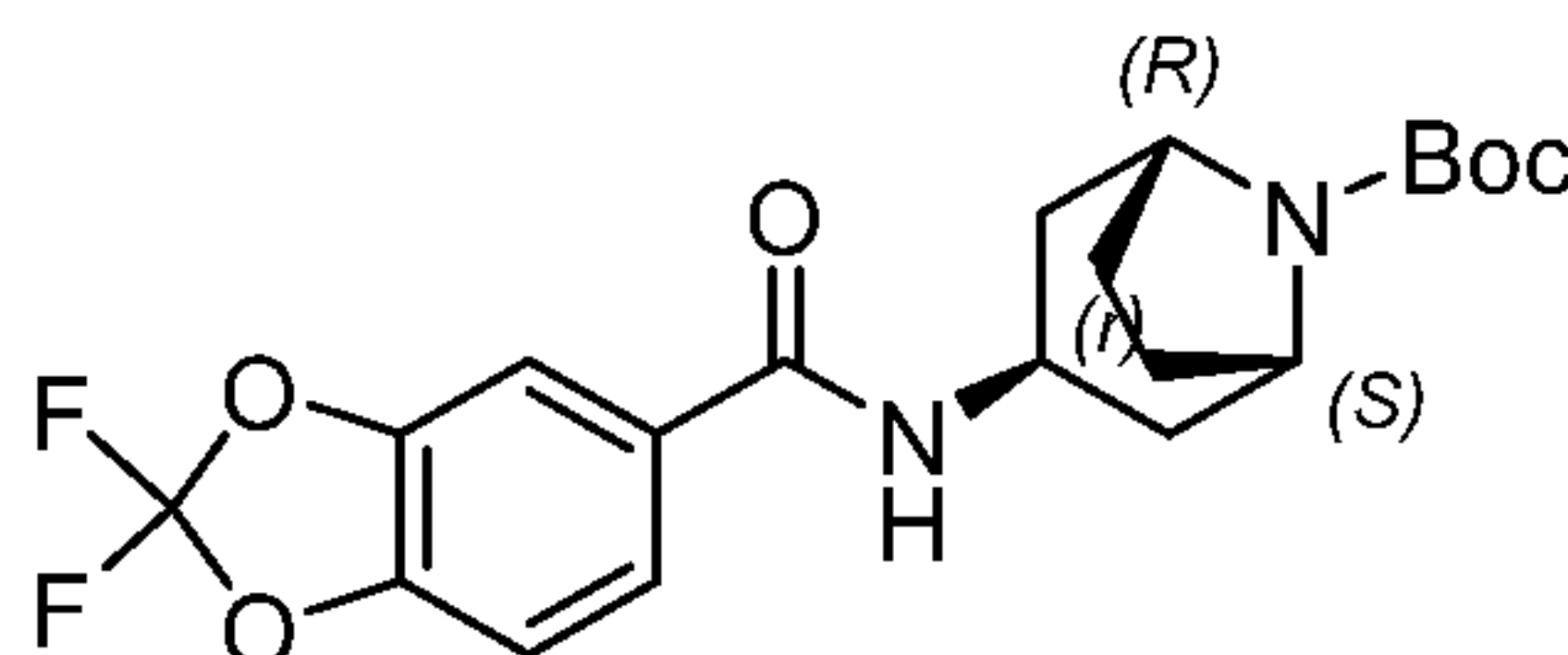
[0311] Into a 100-mL round-bottom flask, was placed N,N-dimethylformamide (10 mL), (1R,3S,5S)-8-([1-(4,4,4-trifluorobutyl)piperidin-4-yl]methane)sulfonyl)-8-azabicyclo[3.2.1]octan-3-amine (50 mg, 0.13 mmol, 1.00 equiv), 6-chloro-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid (46 mg, 0.22 mmol, 1.73 equiv), 1H-1,2,3-benzotriazol-1-ol (35 mg, 0.26 mmol, 2.06 equiv), EDCI (50 mg, 0.26 mmol, 2.07 equiv), TEA (0.3 mL). The resulting solution was stirred for 12 h at 10°C. The solids were filtered out. The resulting mixture was diluted with 10 mL of water. The resulting solution was extracted with of 2x10 mL dichloromethane and the organic layers combined. The organic phase was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude residue was purified by Prep-HPLC with the following conditions (2#-Waters 2767-2(HPLC-08)): Column, Xbridge Prep Phenyl, 5 um, 19x150 mm; mobile phase, Water with 50 mmol ammonium bicarbonate and acetonitrile (10.0% acetonitrile up to 33.0% in 2 min, up to 53.0% in 8 min, up to 100.0% in 1 min, down to 10.0% in 1 min); Detector, UV 254 nm. This resulted in 5.7 mg (8%) of 6-chloro-2-oxo-N-[(1R,3S,5S)-8-([1-(4,4,4-trifluorobutyl)piperidin-4-yl]methane)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-2,3-dihydro-1H-indole-5-carboxamide as a light pink solid. ¹HNMR (300 MHz, CD₃OD): δ 7.32 (s, 1H), 6.95 (s, 1H), 4.30-4.10 (m, 3H), 3.35 (s, 2H), 3.10-2.90 (m, 4H), 2.50-2.40 (m, 2H), 2.40-1.90 (m, 15H), 1.85-1.70 (m, 2H), 1.51-1.35 (m, 2H) ppm. LCMS (method B, ESI): RT=1.67 min, *m/z* = 591.1 [M+H]⁺.

EXAMPLE 16

Synthesis of N-((1R,3r,5S)-8-(4-aminocyclohexylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide trifluoroacetate (Cpd. No. 622)

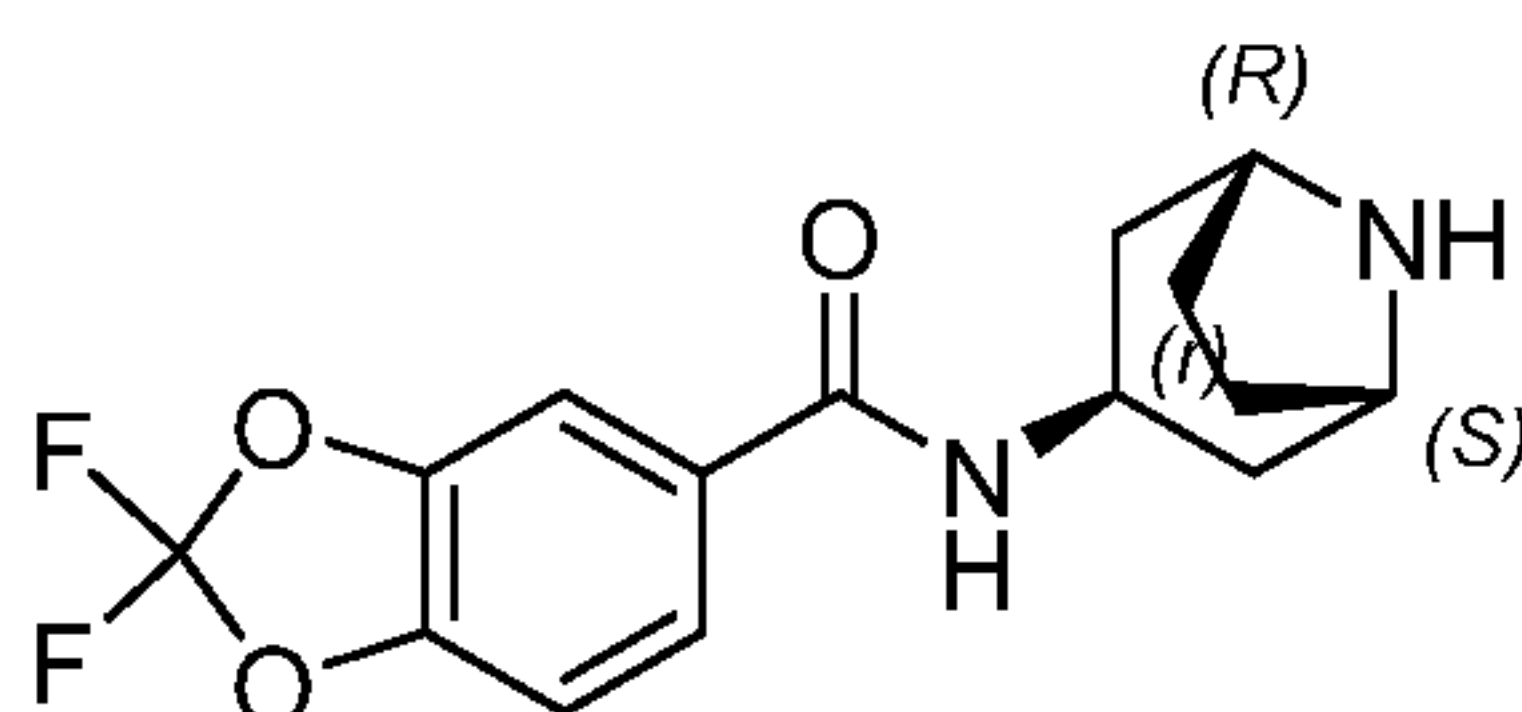


Step 1: Synthesis of tert-butyl (1R,3r,5S)-3-(2,2-difluoro-2H-1,3-benzo[d][1,3]dioxole-5-carboxamido)-8-azabicyclo[3.2.1]octane-8-carboxylate



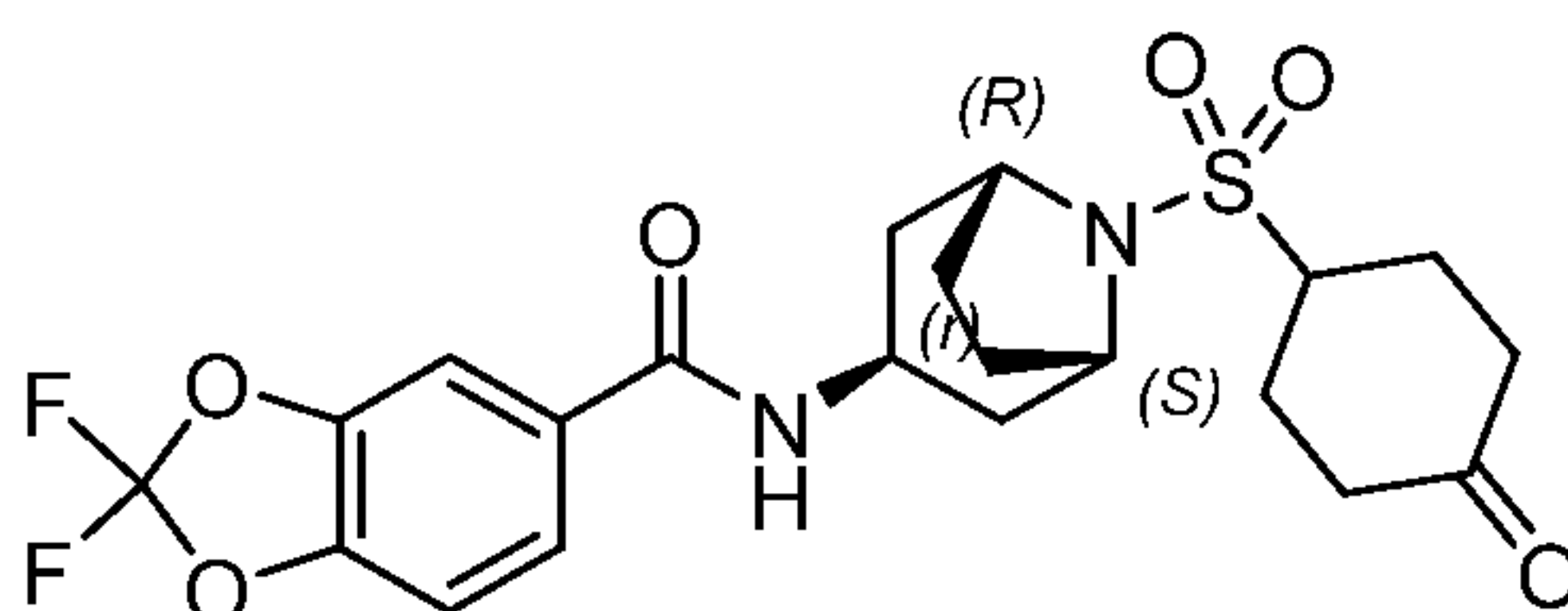
[0312] Into a 100-mL round-bottom flask was placed dichloromethane (50 mL), 2,2-difluoro-2H-1,3-benzo[d][1,3]dioxole-5-carboxylic acid (1.5 g, 7.42 mmol, 1.00 equiv), tert-butyl (1R,5S,7S)-7-amino-3-azabicyclo[3.3.2]decane-3-carboxylate (2.0 g, 7.86 mmol, 1.06 equiv), HATU (5.65 g), and TEA (2.25 g, 22.24 mmol, 3.00 equiv). The resulting solution was stirred for 12 h at 25°C. The resulting mixture was washed with 3x50 mL of H₂O. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was chromatographed on a silica gel column with PE: EA (1:1). This resulted in 3.0 g (92%) of tert-butyl(1R,5r,7S)-7-(2,2-difluoro-2H-1,3-benzo[d][1,3]dioxole-5-carboxamido)-3-azabicyclo[3.3.2]decane-3-carboxylate as a white solid. ¹HNMR (300 MHz, DMSO): δ 8.20-8.15 (m, 1H), 7.77 (s, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 4.08-3.90 (m, 1H), 3.50-3.10 (m, 2H), 2.15-1.80 (m, 8H), 1.50-1.30 (m, 9H) *ppm*. LCMS (method C, ESI): RT=1.25 min, *m/z* =411.2 [M+H]⁺.

Step 2: Synthesis of N-((1R,3r,5S)-8-aza-bicyclo[3.2.1]octan-3-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide



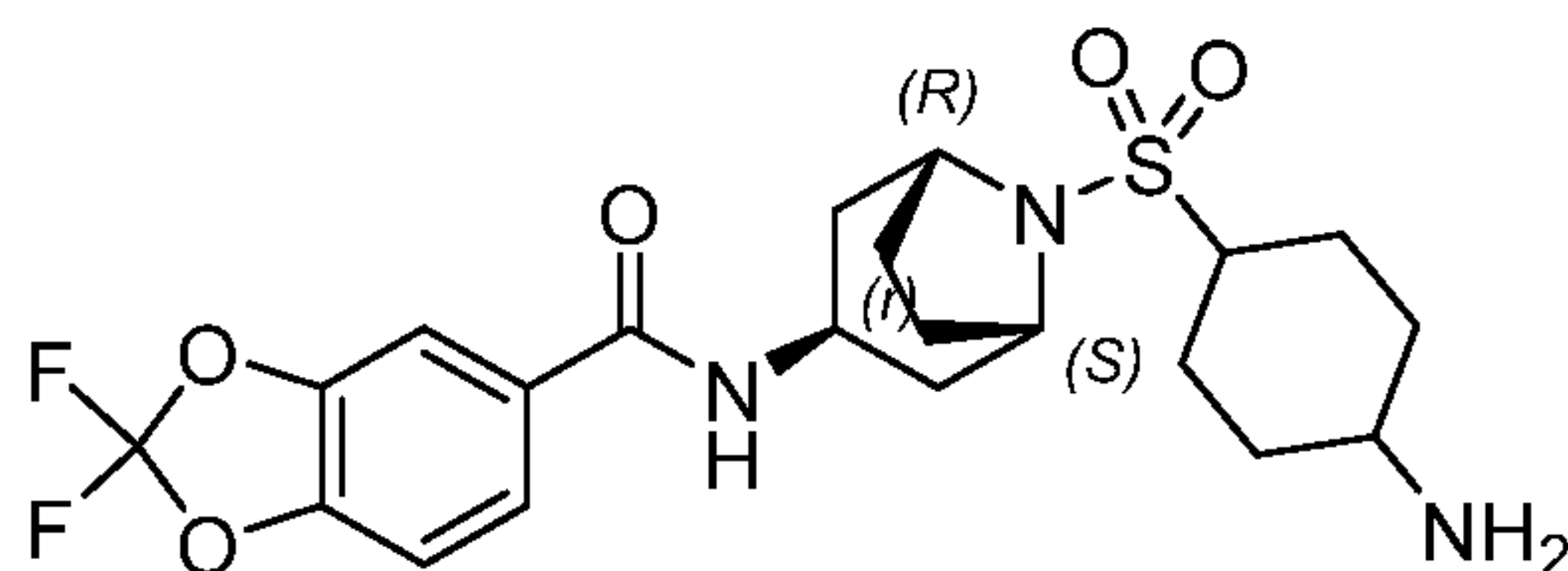
[0313] Into a 100-mL round-bottom flask was placed a solution of tert-butyl (1R,3r,5S)-3-(2,2-difluoro-2H-1,3-benzo[d][1,3]dioxole-5-carboxamido)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.5 g, 3.65 mmol, 1.00 equiv) in methanol (30 mL). Hydrogen chloride gas was introduced into the solution at 0°C for 1 h. The resulting solution was stirred for another 1 h at 20°C. The mixture was then concentrated under vacuum. This resulted in 1.3 g (crude) of N-[(1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl]-2,2-difluoro-2H-1,3-benzo[d][1,3]dioxole-5-carboxamide as a white solid. LCMS (method A, ESI): RT = 0.80 min, *m/z* =311.2 [M+H]⁺.

Step 3: Synthesis of 2,2-difluoro-N-((1R,3r,5S)-8-(4-oxocyclohexylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)benzo[d][1,3]dioxole-5-carboxamide



[0314] Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed a solution of N-[(1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl]-2,2-difluoro-2H-1,3-benzo[d][1,3]dioxole-5-carboxamide (900 mg, 2.90 mmol, 1.00 equiv) in THF (150 mL). This was followed by the addition of LiHMDS (1M in THF, 10 mL) dropwise with stirring at -60°C. To this was added 4-oxocyclohexane-1-sulfonyl chloride (700 mg, 3.56 mmol, 1.23 equiv) in portions at -60°C. The resulting solution was allowed to warm to room temperature and stirred for another 12 hours at 25°C. The resulting mixture was concentrated under vacuum. The residue was extracted with 3x60 mL of dichloromethane and the organic layers combined, dried over anhydrous sodium sulfate and concentrated. The residue was chromatographed on a C18 gel column with H₂O/CH₃CN=3:5. This resulted in 260 mg (19%) of 2,2-difluoro-N-[(1R,3r,5S)-8-[(4-oxocyclohexane)sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-2H-1,3-benzo[d][1,3]dioxole-5-carboxamide as a white solid. LCMS (method B, ESI): RT = 1.08 min, m/z = 471.0 [M+H]⁺.

Step 4: Synthesis of N-((1R,3r,5S)-8-(4-aminocyclohexylsulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide trifluoroacetate

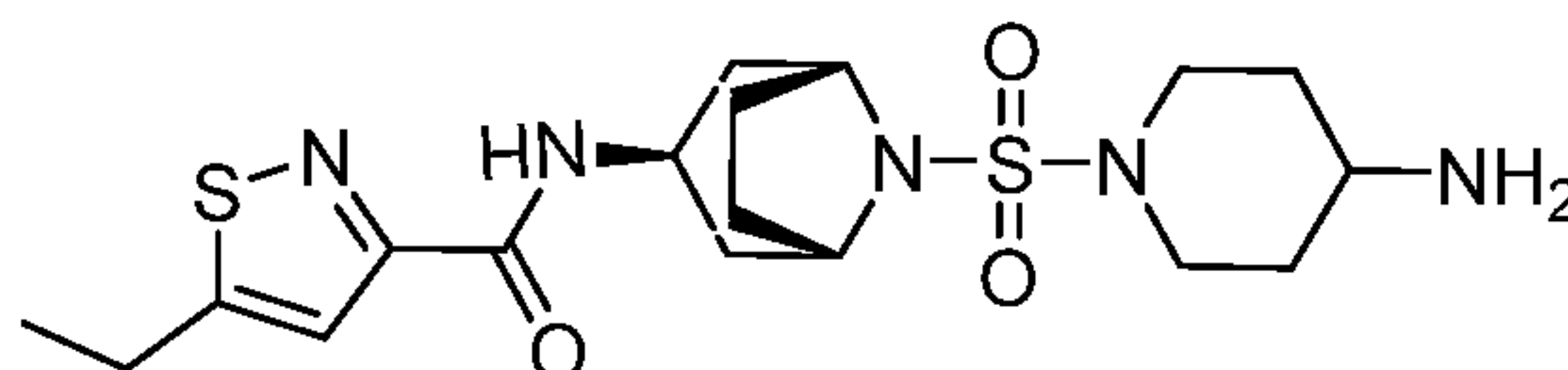


[0315] Into a 250-mL round-bottom flask was placed methanol (130 mL), 2,2-difluoro-N-[(1R,3r,5S)-8-[(4-oxocyclohexane)sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-2H-1,3-benzo[d][1,3]dioxole-5-carboxamide (200 mg, 0.43 mmol, 1.00 equiv), HCOONH₄ (1080 mg, 17.13 mmol, 40.29 equiv), and acetic acid (24 mg, 0.40 mmol, 0.94 equiv). Then NaBH₃CN (50 mg, 0.79 mmol, 1.87 equiv) was added batchwise. The resulting solution was stirred for 2 h at 20°C. The mixture was then concentrated under vacuum. The residue was slurried with 150 mL of EtOAc and then filtrated. The filtrate was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: Column, X Bridge C18, 19*150 mm, 5 um; mobile phase, Mobile Phase A: Water/0.05% TFA, Mobile Phase B: ACN; Flow rate: 20 mL/min; Detector, 254 nm. This resulted in 15.2 mg (6%) of N-[(1R,3r,5S)-8-[(4-aminocyclohexane)sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-2,2-difluoro-2H-1,3-

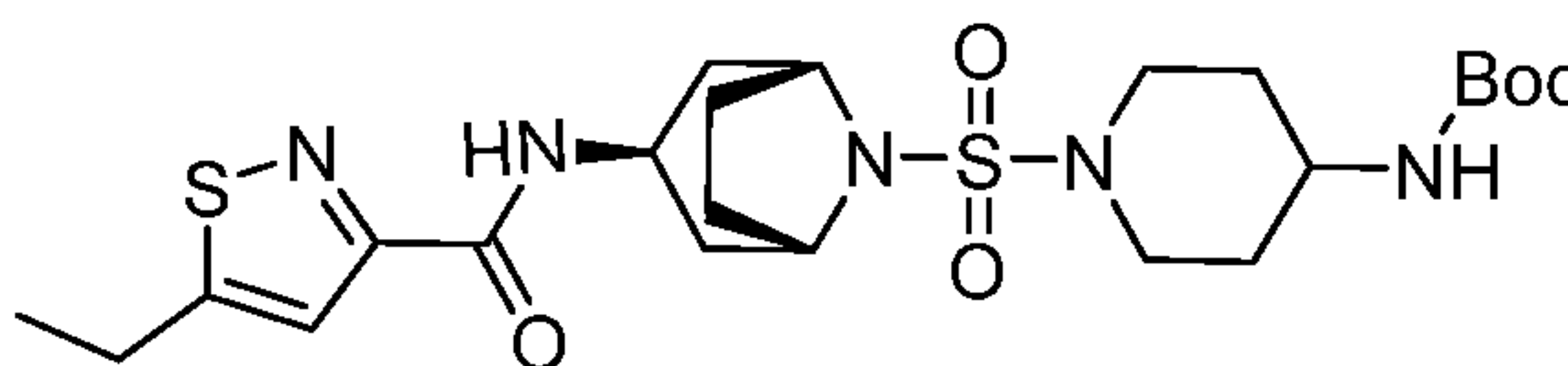
benzo[d][1,3]dioxole-5-carboxamide trifluoroacetic acid as a white solid. ^1H NMR(300 MHz, D_2O): δ 7.46-7.44 (m, 2H), 7.19 (d, $J = 6$ Hz, 1H), 4.18 (s, 2H), 4.05 (t, $J = 6.0$ Hz, 1H), 3.48-3.10 (m, 2H), 2.30-1.80 (m, 13H), 1.65-1.38 (m, 3H) ppm. LCMS (method D, ESI): RT = 1.55 min, $m/z = 472.0$ $[\text{M}+\text{H}]^+$.

EXAMPLE 17

Synthesis of N-[(1R,3r,5S)-8-(4-aminopiperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-5-ethyl-1,2-thiazole-3-carboxamide hydrochloride (Cpd. No. 610)

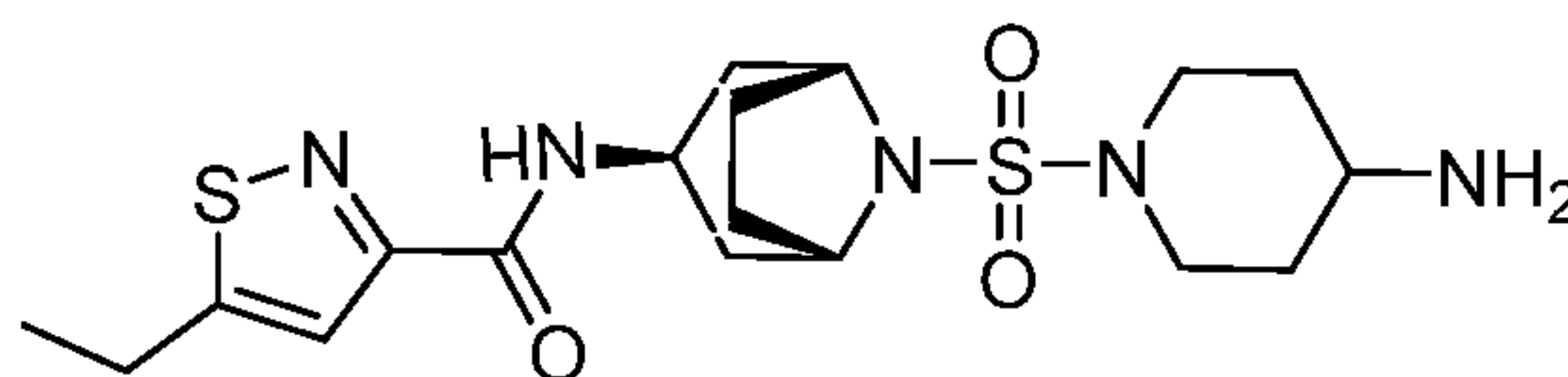


Step 1: Synthesis of tert-butyl N-[1-[(1R,3r,5S)-3-(5-ethyl-1,2-thiazole-3-carboxamido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate



[0316] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed dichloromethane (10 mL), 5-ethyl-1,2-thiazole-3-carboxylic acid (44 mg, 0.28 mmol, 1.00 equiv), tert-butyl N-[1-[(1R,3r,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate (100 mg, 0.34 mmol, 1.21 equiv), HOBT (52 mg, 0.38 mmol, 1.36 equiv), and EDCI (150 mg, 0.79 mmol, 2.80 equiv). This was followed by the addition of a solution of triethylamine (80 mg, 0.79 mmol, 2.80 equiv) in dichloromethane (1 mL) which was added dropwise with stirring at 0°C . The resulting solution was stirred for 15 hours at 20°C . The reaction was quenched by the addition of 50 mL of water and extracted with 2x 100 mL of dichloromethane. The organic layers were combined and washed with 1x50 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (1:2). This resulted in 120 mg (81%) of tert-butyl N-[1-[(1R,3r,5S)-3-(5-ethyl-1,2-thiazole-3-carboxamido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate as a solid. LCMS (method A, ESI): RT = 1.61 min, $m/z = 528.0$ $[\text{M}+\text{H}]^+$.

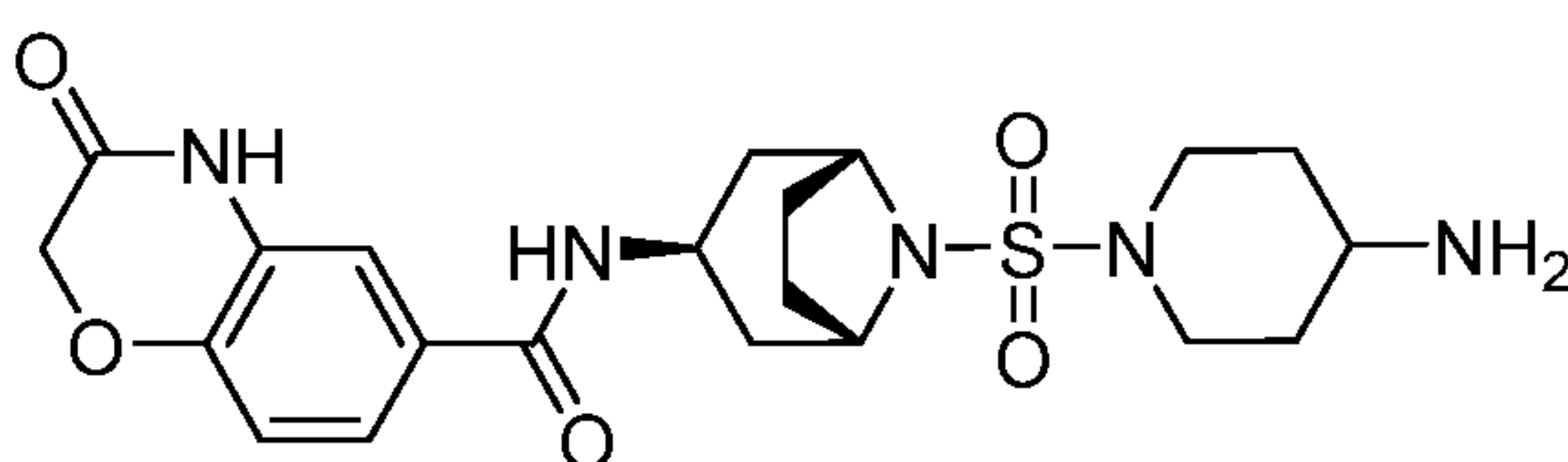
Step 2: Synthesis of N-[(1R,3r,5S)-8-(4-aminopiperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-5-ethyl-1,2-thiazole-3-carboxamide hydrochloride



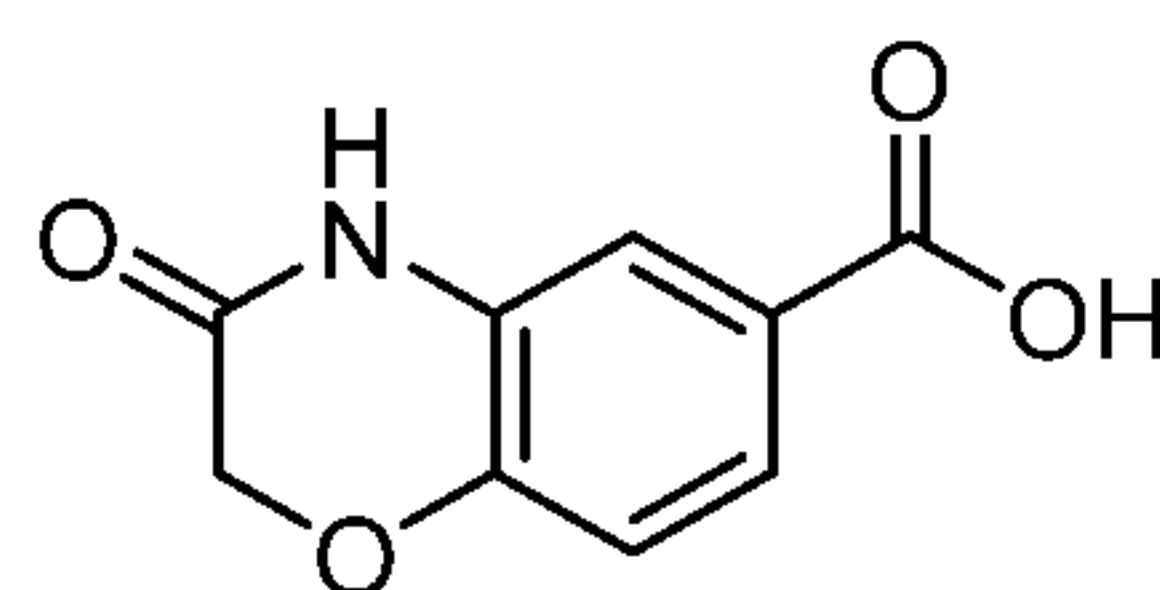
[0317] Into a 50-mL round-bottom flask was placed tert-butyl N-[1-[(1R,3r,5S)-3-(5-ethyl-1,2-thiazole-3-carboxamido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate (120 mg, 0.23 mmol, 1.00 equiv) and hydrogen chloride/dioxane (10 mL, saturated, this solution was made by introducing hydrogen chloride gas into 1,4-dioxane under 0°C for 6 hours). The resulting solution was stirred for 3 hours at 20°C. The mixture was then concentrated under vacuum. This resulted in 57.8 mg (55%) of N-[(1R,3r,5S)-8-(4-aminopiperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-5-ethyl-1,2-thiazole-3-carboxamide hydrochloride as a solid. ¹H NMR (300 MHz, D₂O) δ : 7.45 (s, 1H), 4.15-4.02 (m, 3H), 3.80-3.78 (m, 2H), 3.38-3.22 (m, 1H), 2.98-2.82 (m, 4H), 2.30-2.18 (m, 2H), 2.11-1.87 (m, 8H), 1.71-1.52 (m, 2H), 1.30-1.20 (m, 3H) ppm. LCMS (method A, ESI): RT = 1.81 min, *m/z* = 428.2 [M-HCl+H]⁺.

EXAMPLE 18

Synthesis of N-((1R,3r,5S)-8-(4-aminopiperidin-1-ylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide hydrochloride (Cpd, No. 609)



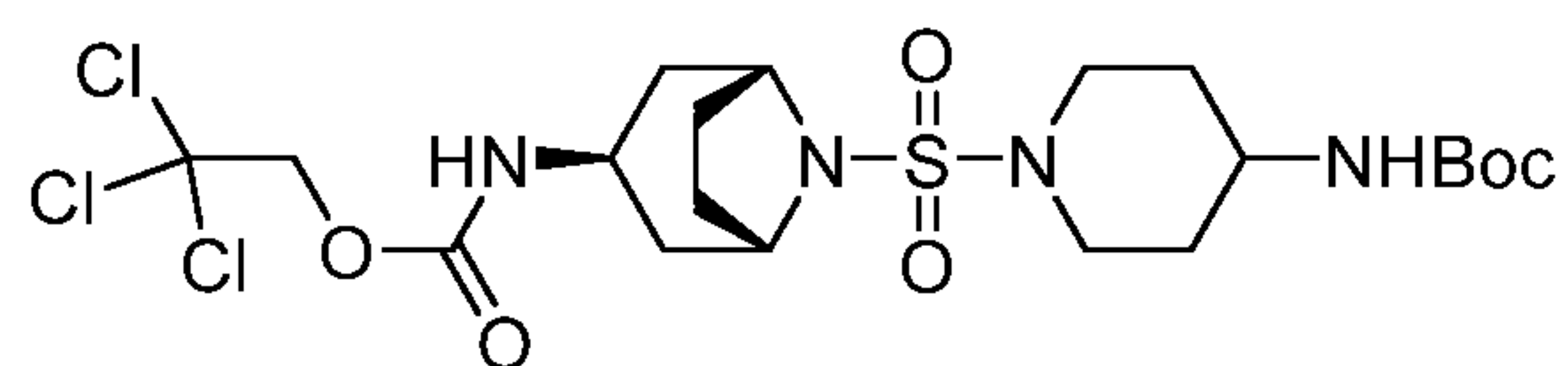
Step 1: Synthesis of 3-oxo-3,4-dihydro-2H-1,4-benzo[b][1,4]oxazine-6-carboxylic acid



[0318] Into a 100-mL round-bottom flask was placed methyl 3-oxo-3,4-dihydro-2H-1,4-benzo[b][1,4]oxazine-6-carboxylate (1 g, 4.83 mmol, 1.00 equiv), methanol (15 mL), tetrahydrofuran (15 mL), and water (15 mL). This was followed by the addition of a solution of sodium hydroxide (386 mg, 9.65 mmol, 2.00 equiv) in 5 mL H₂O which was added dropwise with stirring at 0°C. The solution was stirred for 20 min at 0°C in an ice/salt bath. The resulting solution was allowed to react, with stirring, for an additional

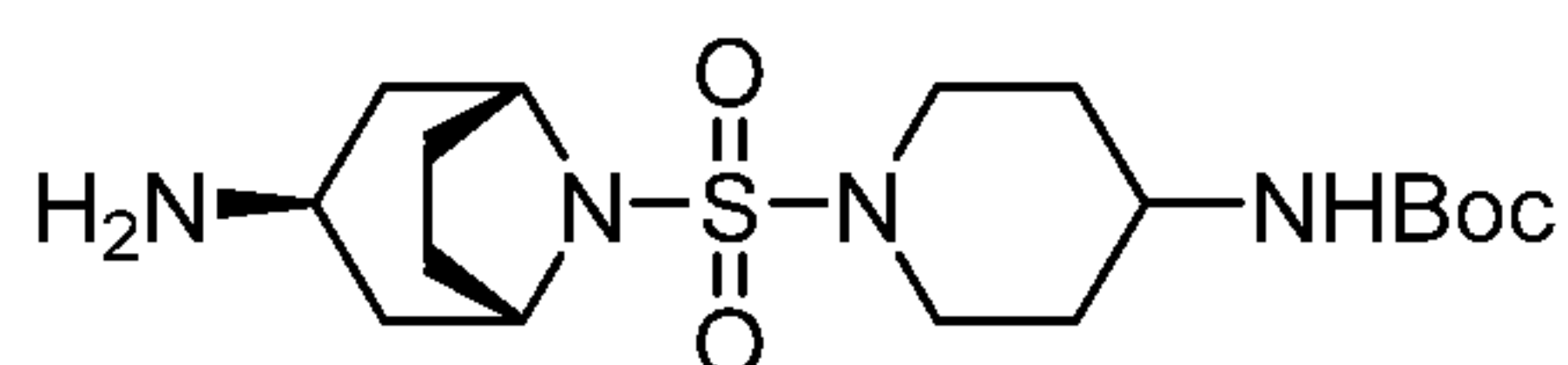
18 h at room temperature. The reaction mixture was then concentrated under vacuum. The residue was diluted with 50 mL of H₂O and The pH adjusted to 3-4 with hydrochloric acid (1 N). The resulting mixture was extracted with 3x50 mL of ethyl acetate. The organic layers were combined and washed with 2x30 mL of water and 1x30 mL of brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and the filtrate concentrated under vacuum. This resulted in 850 mg (91%) of 3-oxo-3,4-dihydro-2H-1,4-benzo[b][1,4]oxazine-6-carboxylic acid as a brown solid.. ¹H NMR (300 MHz, CD₃OD) δ : 7.68 (q, J=8.4Hz, 1H), 7.61 (d, J=1.8Hz, 1H), 7.02 (d, J=8.4Hz, 1H), 4.68 (s, 2H) ppm. LCMS (method A, ESI): RT = 1.01 min, m/z = 194.0 [M+H]⁺.

Step 2: Synthesis of 2,2,2-trichloroethyl N-[(1R,3r,5S)-8-(4-[[[(tert-butoxy)carbonyl]amino]piperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]carbamate



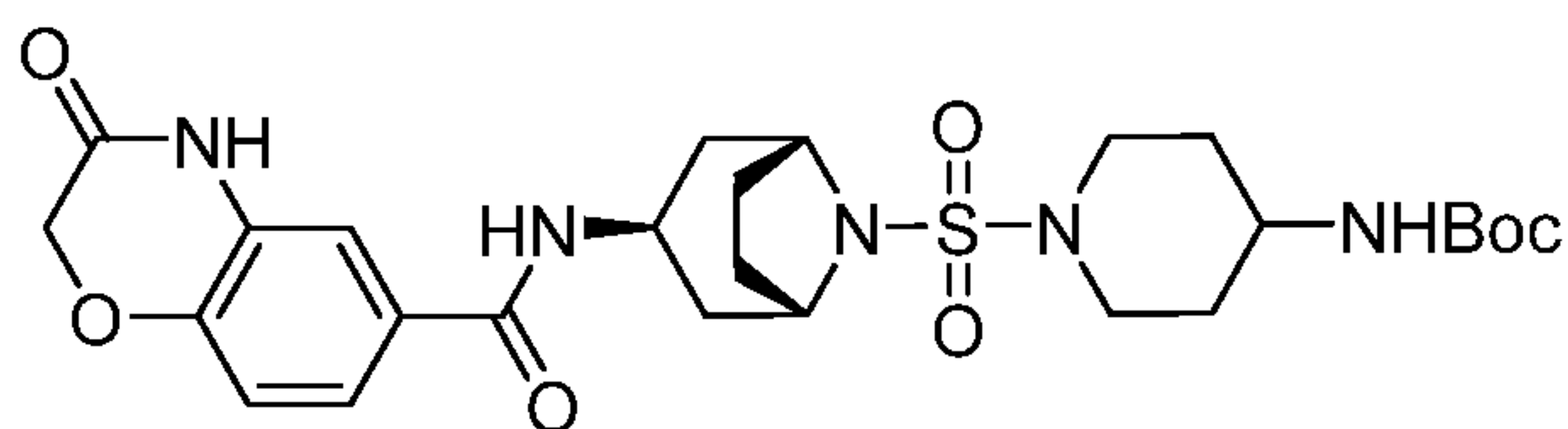
[0319] Into a 100-mL round-bottom flask was placed dichloromethane (30 mL), 2,2,2-trichloroethyl N-[(1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl]carbamate hydrochloride (900 mg, 2.66 mmol, 1.00 equiv), and TEA (1.37 g, 13.54 mmol, 5.00 equiv). This was followed by the addition of a solution of tert-butyl N-[1-(chlorosulfonyl)piperidin-4-yl]carbamate (1.6 g, 5.35 mmol, 2.00 equiv) in 2ml dichloromethane which was added dropwise with stirring at 0°C. The resulting solution was stirred for 14 h at 10°C. The mixture was then washed with 3x30 mL of brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and the filtrate concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 1.1 g (73%) of 2,2,2-trichloroethyl N-[(1R,3r,5S)-8-(4-[[[(tert-butoxy)carbonyl]amino]piperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]carbamate as a white solid. ¹H NMR (400 MHz, CDCl₃) δ : 5.22 (s, 1H), 4.75 (s, 2H), 4.47 (s, 1H), 4.14 (s, 2H), 3.98 (d, J=6Hz, 1H), 3.70 (d, J=12Hz, 2H), 3.58 (s, 1H), 2.84 (t, J=11.2Hz, 2H), 2.27-2.25 (m, 4H), 2.03 (d, J=10.8Hz, 2H), 1.95-1.87 (m, 4H), 1.58 (s, 2H), 1.55-1.40 (m, 9H) ppm. LCMS (method C, ESI): RT = 1.24 min, m/z = 563.0 [M+H]⁺.

Step 3: Synthesis of tert-butyl N-[1-[(1R,3r,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate



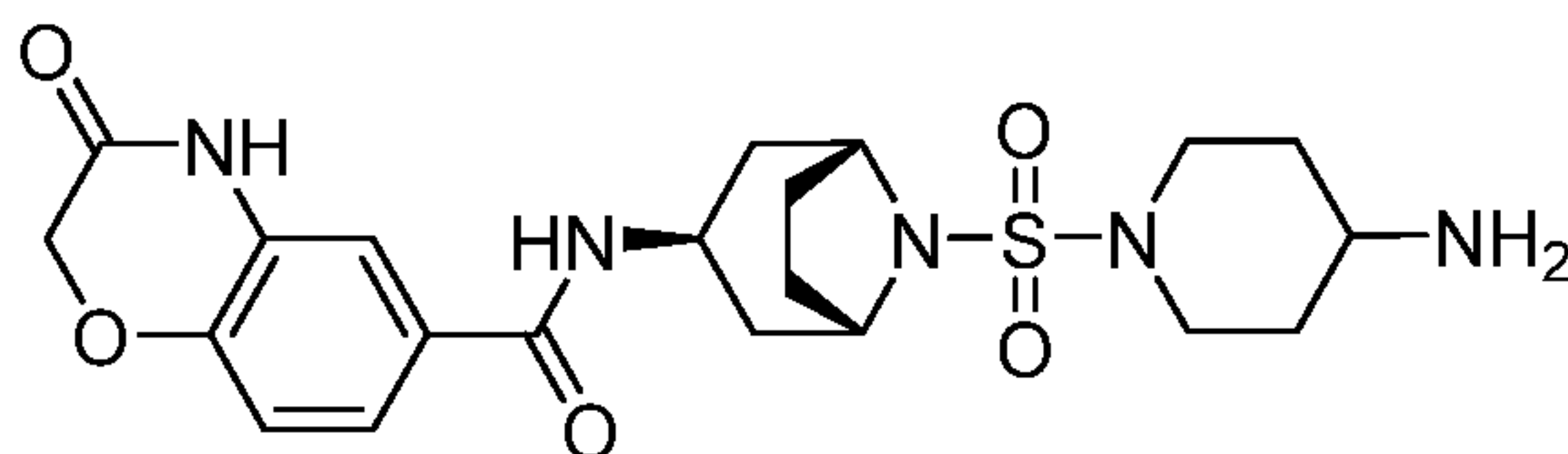
[0320] Into a 100-mL round-bottom flask was placed 2,2,2-trichloroethyl N-[(1R,3r,5S)-8-(4-[[tert-butoxy]carbonyl]amino)piperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]carbamate (1.1 g, 1.95 mmol, 1.00 equiv), Zn (1.9 g, 15.00 equiv), AcOH (15 mL), and water (1 mL). The resulting mixture was stirred for 3 h at 10°C. The solids were filtered out. The pH was adjusted to 8 with sodium carbonate (aq. sat.). The resulting solution was extracted with 4x50 mL of ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. This resulted in 750 mg (crude) of tert-butyl N-[1-[(1R,3r,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate as a light yellow crude solid. LCMS (method C, ESI): RT = 0.61 min, m/z = 389.0 [M+H]⁺.

Step 4: Synthesis of tert-butyl (1-(((1R,3r,5S)-3-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamido)-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)piperidin-4-yl)carbamate



[0321] Into a 100-mL round-bottom flask was placed N,N-dimethylformamide (10 mL), 3-oxo-3,4-dihydro-2H-1,4-benzo[b][1,4]oxazine-6-carboxylic acid (55 mg, 0.28 mmol, 1.10 equiv), EDCI (98 mg, 0.51 mmol, 2.00 equiv), HOBT (70 mg, 0.52 mmol, 2.00 equiv), and tert-butyl N-1-[(1R,3r,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-ylcarbamate (100 mg, 0.26 mmol, 1.00 equiv). This was followed by the addition of TEA (131 mg, 1.29 mmol, 5.00 equiv) which was added dropwise with stirring at 0°C. The resulting solution was stirred for 15 h at 10°C. The reaction mixture was diluted with 10 mL of H₂O and extracted with 3x10 mL of ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was chromatographed on a silica gel column with dichloromethane/methanol (10:1). This resulted in 100 mg (69%) of tert-butyl N-[1-[(1R,3r,5S)-3-(3-oxo-3,4-dihydro-2H-1,4-benzo[b][1,4]oxazine-6-carboxamido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate as a white solid. LCMS (method A, ESI): RT = 1.32 min, m/z = 586.0 [M + Na]⁺.

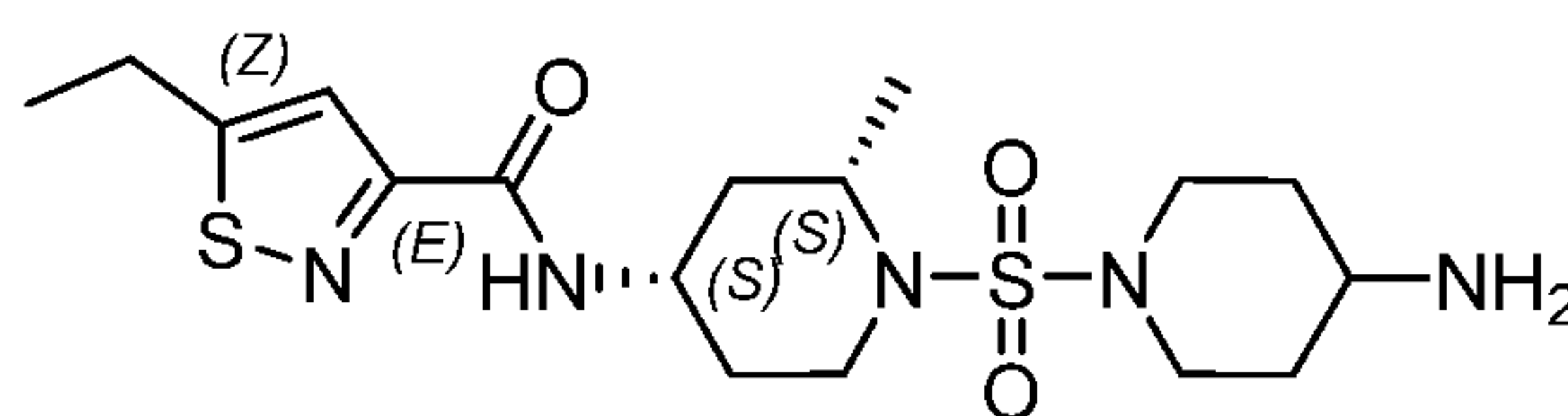
Step 5: Synthesis of N-((1R,3r,5S)-8-(4-aminopiperidin-1-ylsulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide hydrochloride



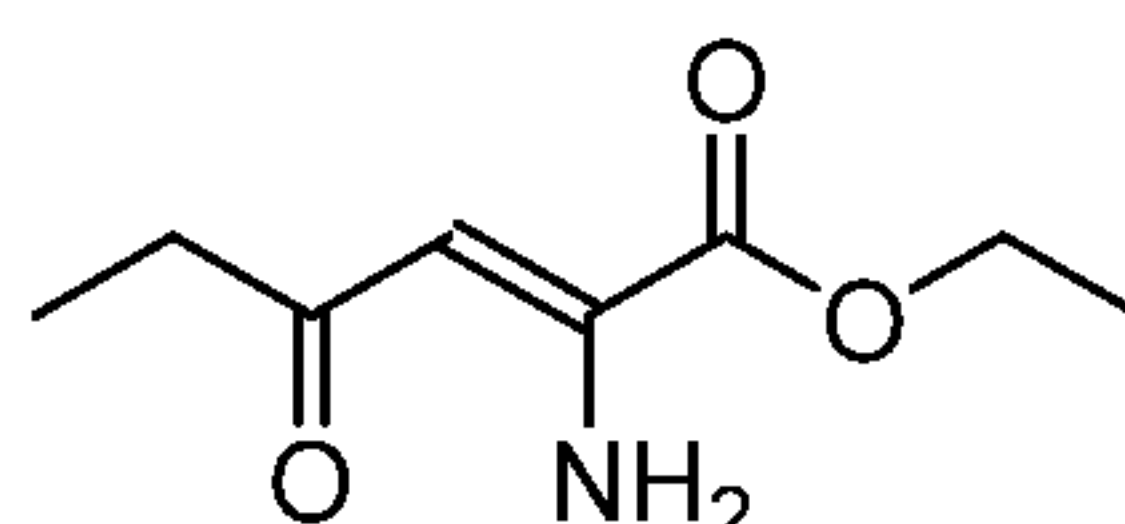
[0322] Into a 50-mL round-bottom flask was placed dichloromethane (10 mL) and tert-butyl N-[1-[(1R,3r,5S)-3-(3-oxo-3,4-dihydro-2H-1,4-benzo[b][1,4]oxazine-6-carboxamido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate (100 mg, 0.18 mmol, 1.00 equiv). To the above hydrogen chloride (gas) was introduced. The resulting solution was stirred for 3 h at 10°C. The reaction mixture was then concentrated under vacuum. The crude product (80 mg) was purified by Prep-HPLC with the following conditions (Prep_HPLC_MC5): Column, X Select C18, 19*250 mm, 5 μ m; mobile phase, A: Water/0.05% TFA, Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 5%B to 36%B in 12.5 min; Detector, 254nm. The isolated purified product was dissolved in 2ml concentrated hydrochloric acid and this solution concentrated under vacuum. This resulted in 45.7 mg (52%) of N-[(1R,3r,5S)-8-(4-aminopiperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-3-oxo-3,4-dihydro-2H-1,4-benzo[b][1,4]oxazine-6-carboxamide hydrochloride as a white solid. ^1H NMR (400 MHz, D_2O) δ : 7.28 (q, J = 8.4Hz, 1H), 7.18 (s, 1H), 6.98 (d, J = 8.4Hz, 1H), 4.60 (s, 2H), 4.10-3.95 (m, 3H), 3.74 (d, J = 13.2Hz, 2H), 3.35-3.25 (m, 1H), 2.88 (t, J = 12Hz, 2H), 2.25-2.18 (m, 2H), 2.10-1.98 (m, 6H), 1.91 (d, J = 14.8Hz, 2H), 1.67-1.52 (m, 2H) ppm. LCMS (method A, ESI): RT =1.40 min, m/z = 464.0 $[\text{M}-\text{HCl}+\text{H}]^+$.

EXAMPLE 19

Synthesis of N-((2S,4S)-1-(4-aminopiperidin-1-ylsulfonyl)-2-methylpiperidin-4-yl)-5-ethyl-1,2-thiazole-3-carboxamide hydrochloride (Cpd. No. 605)



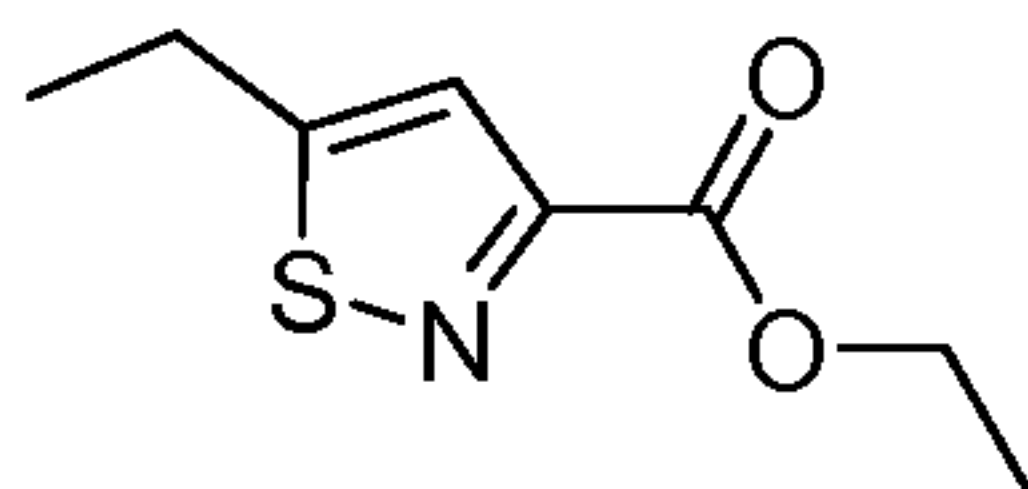
Step 1: Synthesis of ethyl 2-amino-4-oxohex-2-enoate



[0323] Into a 250-mL round-bottom flask was placed ethyl 2,4-dioxohexanoate (10 g, 58.08 mmol, 1.00 equiv), benzene (100 mL), $\text{CH}_3\text{COONH}_4$ (13.4 g, 173.84 mmol, 2.99

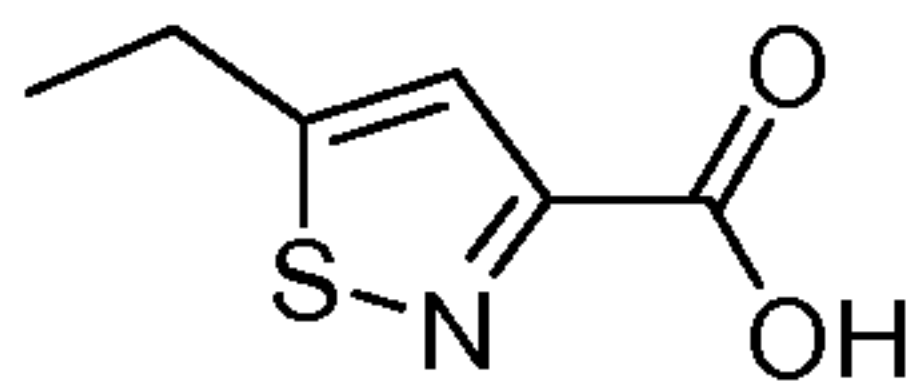
equiv), and acetic acid (10 mL). The resulting solution was stirred at 80°C overnight. The reaction mixture was cooled and concentrated under vacuum. The residue was diluted with 200 mL of ice-water and the pH adjusted to 8 with Na₂CO₃ (aq. Sat.). The resulting mixture was extracted with 3x100 mL of ethyl acetate and the organic layers combined, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (1:10-1:5). This resulted in 7 g (70%) of ethyl 2-amino-4-oxohex-2-enoate as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ : 5.92 (s, 1H), 4.36-4.30 (m, 2H), 2.49-2.44 (m, 2H), 1.28-1.24 (m, 3H), 1.14-1.11 (m, 3H) *ppm*.

Step 2: Synthesis of ethyl 5-ethyl-1,2-thiazole-3-carboxylate



[0324] Into a 250-mL round-bottom flask was placed ethyl 2-amino-4-oxohex-2-enoate (4 g, 23.37 mmol, 1.00 equiv), tetrahydrofuran (50 mL), and P₂S₅ (2.6 g, 11.70 mmol, 0.50 equiv). The mixture was stirred overnight at room temperature. Then the mixture was concentrated and the residue was dissolved in ethyl acetate (20 mL). This solution was cooled to 0°C and H₂O₂ (30%, 10 mL) was added dropwise. The resulting mixture was stirred for 10 min at room temperature. To the mixture was added activated charcoal. After filtration, the filtrate was diluted with H₂O (20 mL). This was extracted with EA (20mLx3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 2.44 g (56%) of ethyl 5-ethyl-1,2-thiazole-3-carboxylate as brown oil. LCMS (method A, ESI): RT =1.36 min, *m/z* = 186.1 [M+H]⁺.

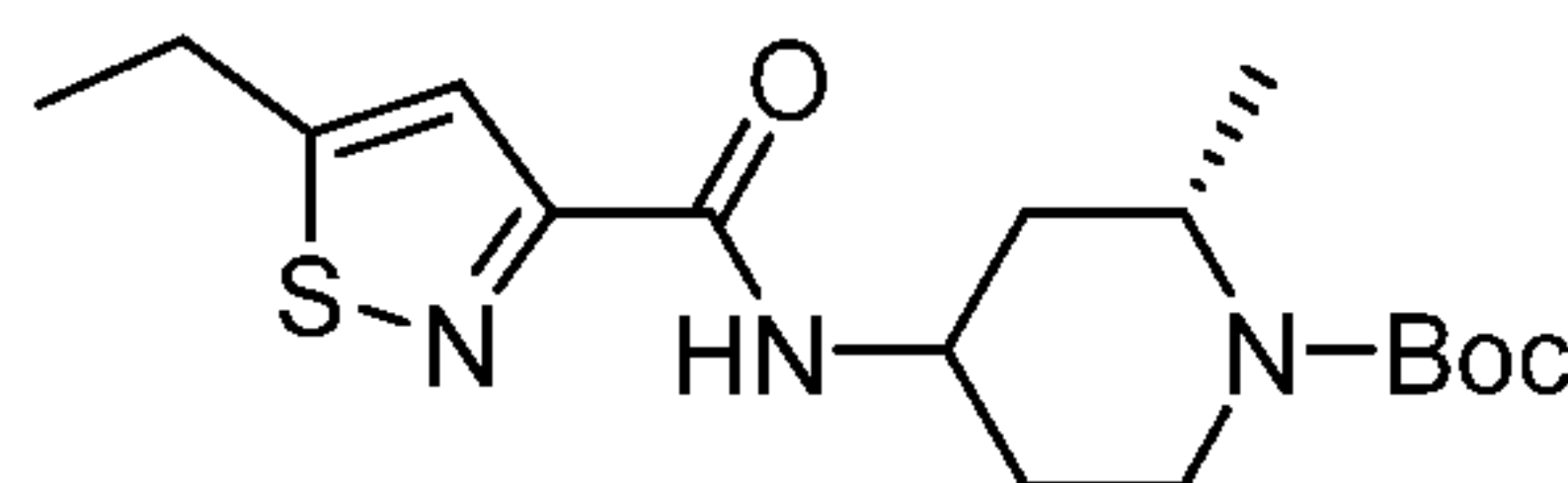
Step 3: Synthesis of 5-ethyl-1,2-thiazole-3-carboxylic acid



[0325] Into a 100-mL round-bottom flask was placed ethyl 5-ethyl-1,2-thiazole-3-carboxylate (2.44 g, 13.17 mmol, 1.00 equiv), methanol (10 mL), water (10 mL), tetrahydrofuran (10 mL) and LiOH.H₂O (1.66 g, 39.56 mmol, 3.00 equiv). The resulting solution was stirred for 1 h at room temperature. The reaction mixture was then concentrated under vacuum. The residue was diluted with 30 mL of H₂O and extracted with 5x30 mL of dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 1.44 g (70%)

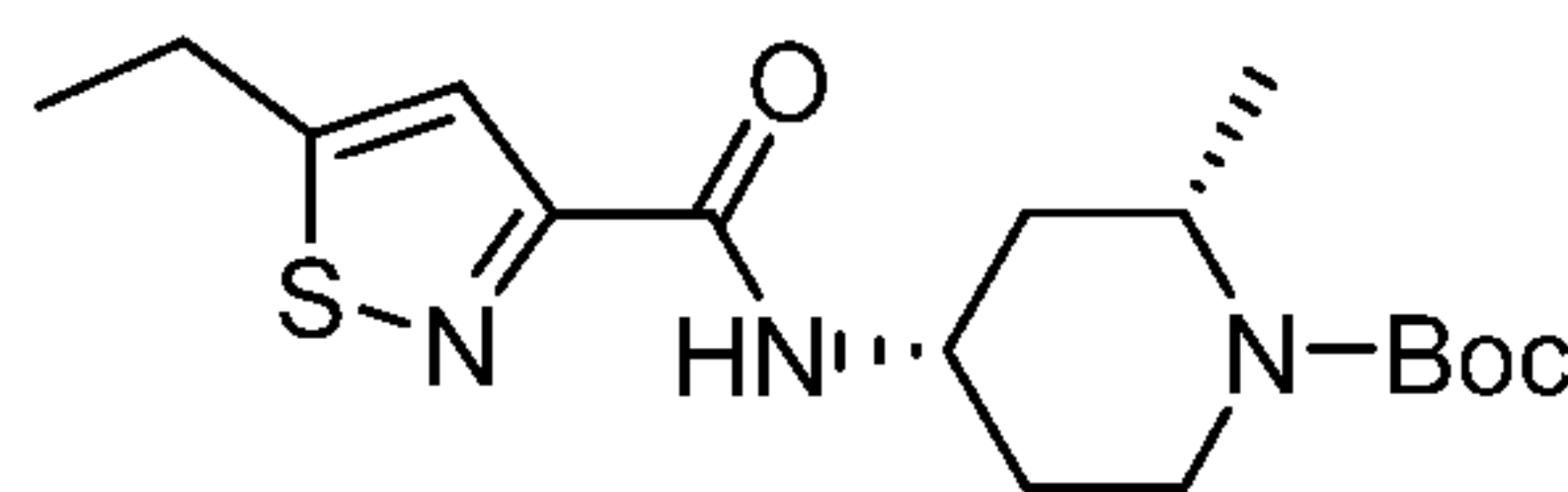
of 5-ethyl-1,2-thiazole-3-carboxylic acid as a brown solid. ^1H NMR (400 MHz, CDCl_3) δ : 7.63 (s, 1H), 3.04-2.96 (m, 2H), 1.42-1.19 (m, 3H) *ppm*. LCMS (method D, ESI): RT =1.09 min, m/z = 158.2 $[\text{M}+\text{H}]^+$.

Step 4: Synthesis of (2S)-tert-butyl 4-(5-ethyl-1,2-thiazole-3-carboxamido)-2-methylpiperidine-1-carboxylate



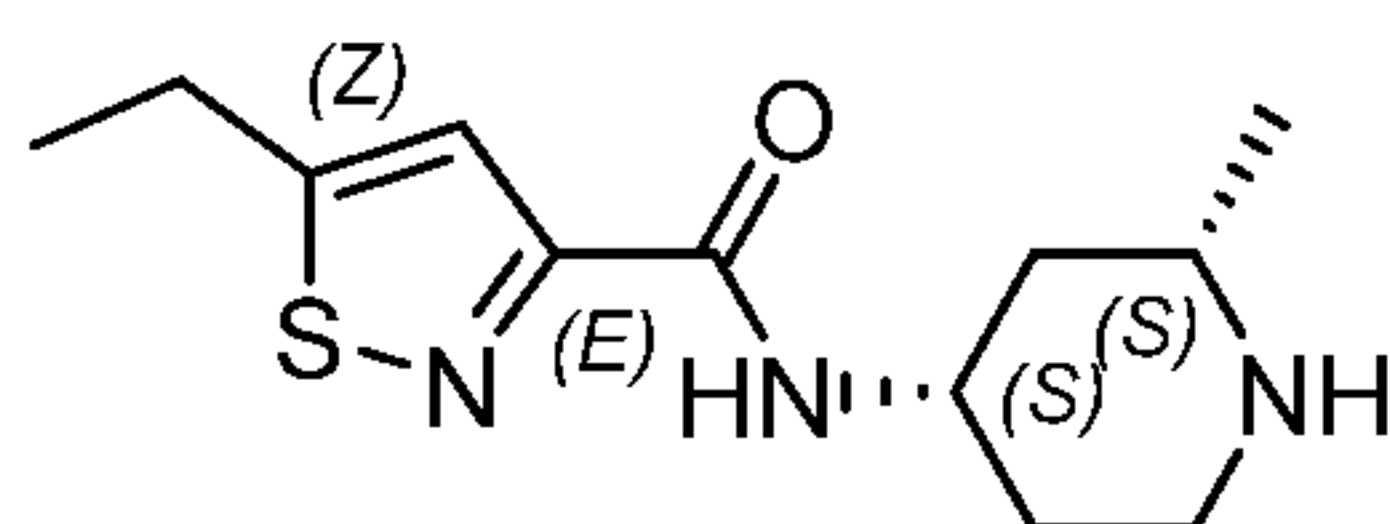
[0326] Into a 250-mL round-bottom flask was placed 5-ethyl-1,2-thiazole-3-carboxylic acid (1.5 g, 9.54 mmol, 1.00 equiv), EDCI (2.92 g, 15.23 mmol, 1.60 equiv), 1H-1,2,3-benzotriazol-1-ol (2.1 g, 15.54 mmol, 1.63 equiv), dichloromethane (20 mL), and (2S)-tert-butyl 4-amino-2-methylpiperidine-1-carboxylate (2.45 g, 11.43 mmol, 1.20 equiv). Then TEA (2.89 g, 28.56 mmol, 2.99 equiv) was added dropwise. The resulting solution was stirred overnight at room temperature. The reaction mixture was diluted with 30 mL of H_2O and extracted with 3x30 mL of dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was chromatographed on a combi-flash with eluent (EA:PE=1/1). This resulted in 1.5 g of (2S)-tert-butyl 4-(5-ethyl-1,2-thiazole-3-carboxamido)-2-methylpiperidine-1-carboxylate as a brown oil. LCMS (method D, ESI): RT =1.60 min, m/z =376.1 $[\text{M}+\text{Na}]^+$.

Step 5: Synthesis of (2S,4S)-tert-butyl 4-(5-ethyl-1,2-thiazole-3-carboxamido)-2-methylpiperidine-1-carboxylate



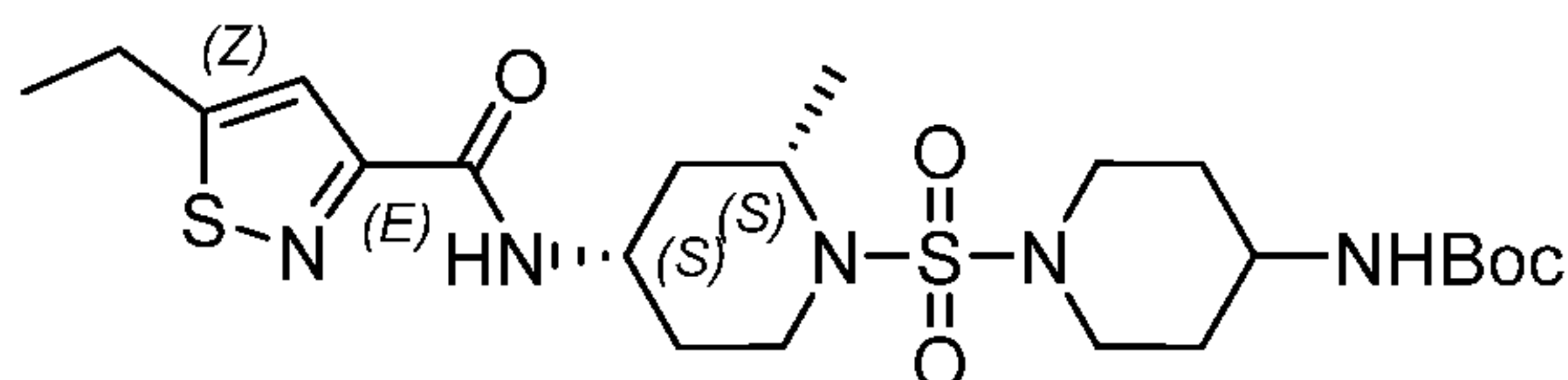
[0327] tert-Butyl (2S)-4-(5-ethyl-1,2-thiazole-3-carboxamido)-2-methylpiperidine-1-carboxylate (470 mg, 1.33 mmol, 1.00 equiv) was purified by Chiral-Prep-HPLC with the following conditions: Column, CHIRALCEL OJ-3, mobile phase, Hex(0.2%IPA) : EtOH=70:30; Detector, 254nm. This resulted in 200 mg (43%) of tert-butyl (2S,4S)-4-(5-ethyl-1,2-thiazole-3-carboxamido)-2-methylpiperidine-1-carboxylate as a yellow solid. ee value: 100%

Step 6: Synthesis of 5-ethyl-N-((2S,4S)-2-methylpiperidin-4-yl)-1,2-thiazole-3-carboxamide



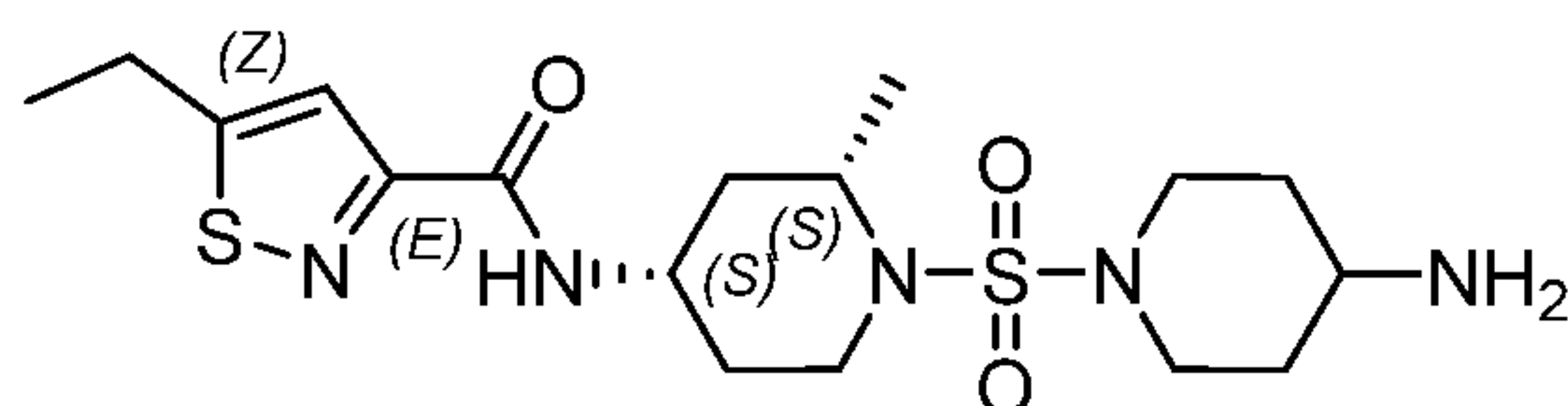
[0328] Into a 25-mL round-bottom flask was placed tert-butyl (2S,4S)-4-(5-ethyl-1,2-thiazole-3-carboxamido)-2-methylpiperidine-1-carboxylate (200 mg, 0.57 mmol, 1.00 equiv), dichloromethane (10 mL). To the above hydrogen chloride (gas) was introduced. The resulting solution was stirred for 1 h at room temperature. The resulting mixture was then concentrated under vacuum. This resulted in 150 mg (91%) of 5-ethyl-N-[(2S,4S)-2-methylpiperidin-4-yl]-1,2-thiazole-3-carboxamide hydrochloride as a white solid. LCMS (method C, ESI): RT = 0.49 min, m/z = 254.4 $[M-HCl+H]^+$.

Step 7: Synthesis of tert-butyl 1-((2S,4S)-4-(5-ethyl-1,2-thiazole-3-carboxamido)-2-methylpiperidin-1-ylsulfonyl)piperidin-4-ylcarbamate



[0329] Into a 25-mL round-bottom flask was placed 5-ethyl-N-[(2S,4S)-2-methylpiperidin-4-yl]-1,2-thiazole-3-carboxamide hydrochloride (150 mg, 0.52 mmol, 1.00 equiv) and dichloromethane (10 mL). Then TEA (260 mg, 5.00 equiv) added dropwise followed by tert-butyl N-[1-(chlorosulfonyl)piperidin-4-yl]carbamate (750 mg, 2.51 mmol, 4.85 equiv) which was added in several portions. The resulting mixture was stirred for 2 h at room temperature. The mixture was concentrated under vacuum and the residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (1/1). This resulted in 150 mg (56%) of tert-butyl N-[1-[(2S,4S)-4-(5-ethyl-1,2-thiazole-3-amido)-2-methylpiperidine-1-sulfonyl]piperidin-4-yl]carbamate as a yellow solid. LCMS (method C, ESI): RT = 1.57 min, m/z = 516.2 $[M+H]^+$.

Step 8: Synthesis of N-((2S,4S)-1-(4-aminopiperidin-1-ylsulfonyl)-2-methylpiperidin-4-yl)-5-ethyl-1,2-thiazole-3-carboxamide hydrochloride

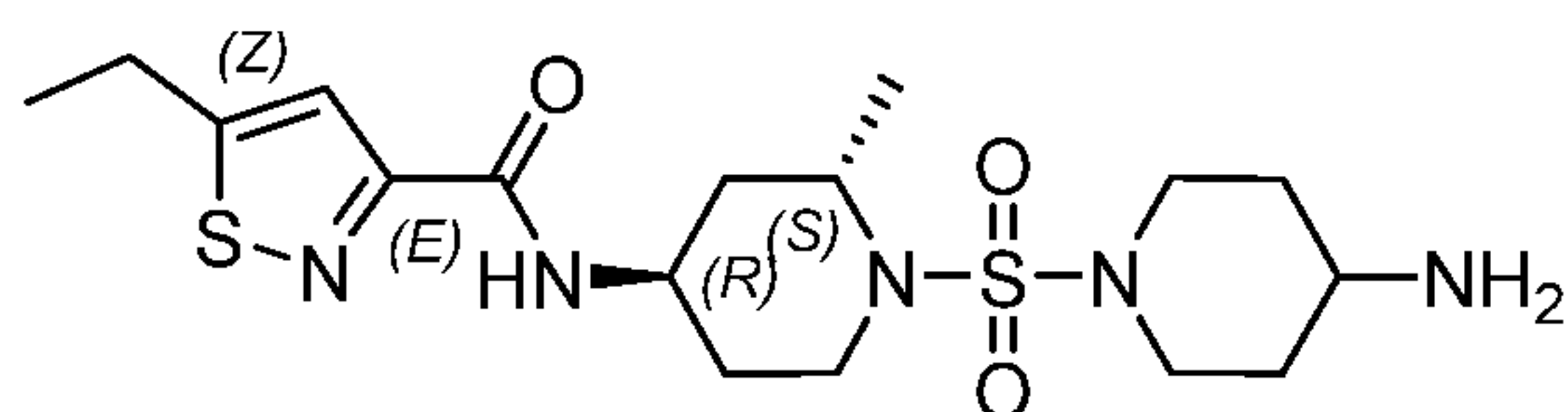


[0330] Into a 25-mL round-bottom flask was placed tert-butyl N-[1-[(2S,4S)-4-(5-ethyl-1,2-thiazole-3-carboxamido)-2-methylpiperidine-1-sulfonyl]piperidin-4-yl]carbamate (150 mg, 0.29 mmol, 1.00 equiv) and dichloromethane (10 mL). To the above hydrogen

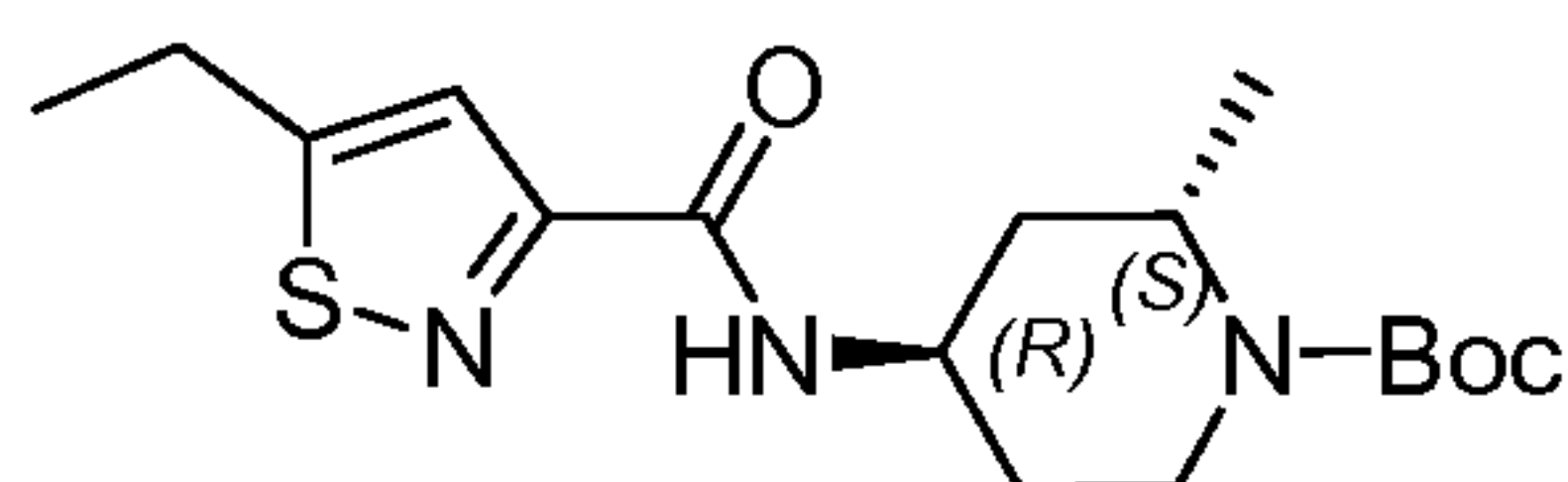
chloride (gas) was introduced. The resulting solution was stirred for 1 h at room temperature. The mixture was then concentrated under vacuum. This resulted in 90 mg (68%) of N-[(2S,4S)-1-(4-aminopiperidine-1-sulfonyl)-2-methylpiperidin-4-yl]-5-ethyl-1,2-thiazole-3-carboxamide hydrochloride as a white solid. ^1H NMR (300 MHz, D_2O) δ : 7.46 (s, 1H), 4.06-4.01 (m, 1H), 3.71-3.55 (m, 4H), 3.33-3.20 (m, 2H), 2.95-2.82 (m, 4H), 2.04-1.97 (m, 4H), 1.80-1.57 (m, 4H), 1.30-1.22 (m, 6H) ppm. LCMS (method A, ESI): RT = 1.74 min, m/z = 416.2 $[\text{M}-\text{HCl}+\text{H}]^+$.

EXAMPLE 20

Synthesis of N-((2S,4R)-1-(4-aminopiperidin-1-ylsulfonyl)-2-methylpiperidin-4-yl)-5-ethyl-1,2-thiazole-3-carboxamide (Cpd. No. 629)

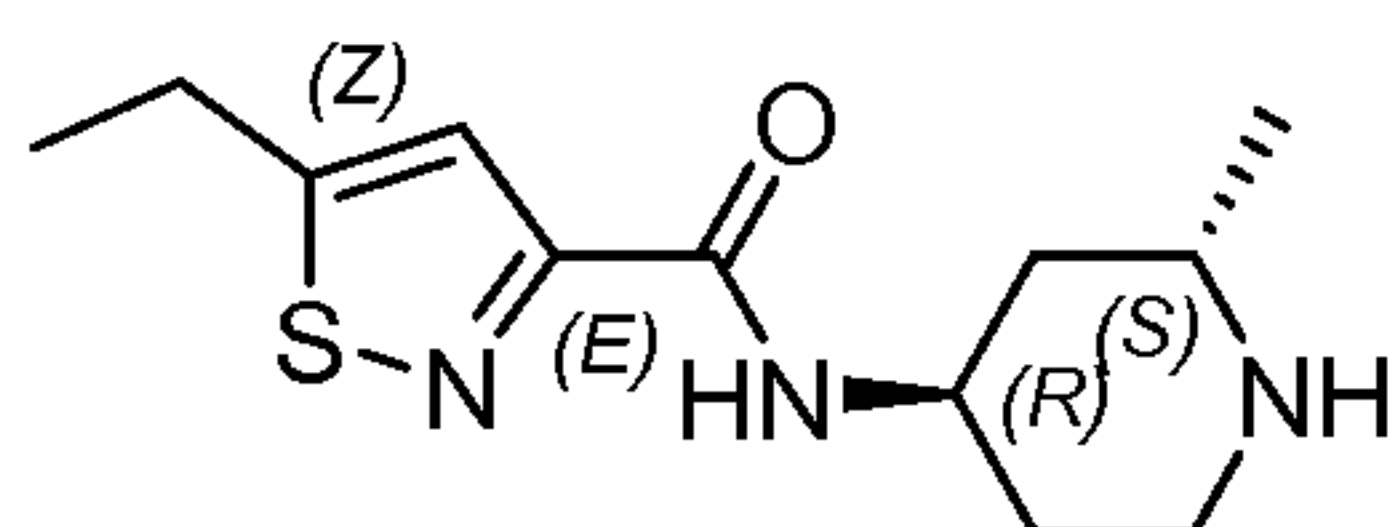


Step 1: Synthesis of (2S,4R)-tert-butyl 4-(5-ethyl-1,2-thiazole-3-carboxamido)-2-methylpiperidine-1-carboxylate



[0331] tert-Butyl (2S)-4-(5-ethyl-1,2-thiazole-3-carboxamido)-2-methylpiperidine-1-carboxylate (470 mg, 1.33 mmol, 1.00 equiv) was purified by Chiral-Prep-HPLC with the following conditions: Column: CHIRALCEL OJ-3-; mobile phase, Hex(0.2%IPA): EtOH=70:30 ; Detector, 254nm. This resulted in 100 mg (21%) of tert-butyl (2S,4R)-4-(5-ethyl-1,2-thiazole-3-amido)-2-methylpiperidine-1-carboxylate as a yellow solid. ee value: 100%.

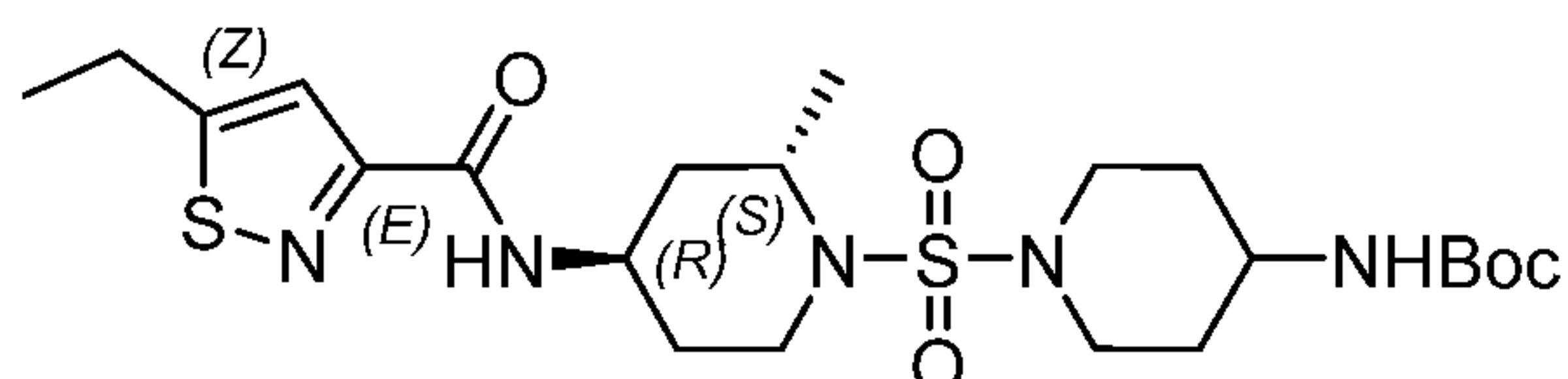
Step 2: Synthesis of 5-ethyl-N-((2S,4R)-2-methylpiperidin-4-yl)-1,2-thiazole-3-carboxamide



[0332] Into a 25-mL round-bottom flask was placed tert-butyl (2S,4R)-4-(5-ethyl-1,2-thiazole-3-carboxamido)-2-methylpiperidine-1-carboxylate (100 mg, 0.28 mmol, 1.00 equiv) and dichloromethane (10 mL). To the above hydrogen chloride (gas) was introduced. The resulting solution was stirred for 1 h at room temperature. The mixture

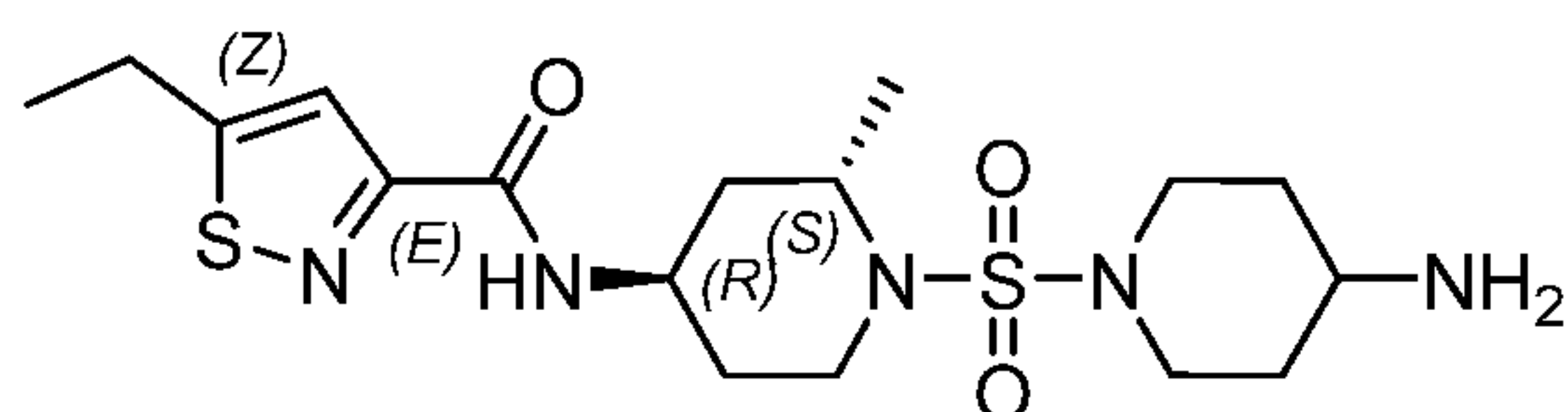
was concentrated under vacuum. This resulted in 70 mg (85%) of 5-ethyl-N-[(2S,4R)-2-methylpiperidin-4-yl]-1,2-thiazole-3-carboxamide hydrochloride as a white solid. LCMS (method C, ESI): RT =0.49 min, m/z = 254.2 $[M-HCl+H]^+$.

Step 3: Synthesis of tert-butyl 1-((2S,4R)-4-(5-ethyl-1,2-thiazole-3-carboxamido)-2-methylpiperidin-1-ylsulfonyl)piperidin-4-ylcarbamate



[0333] Into a 25-mL round-bottom flask was placed 5-ethyl-N-[(2S,4R)-2-methylpiperidin-4-yl]-1,2-thiazole-3-carboxamide hydrochloride (70 mg, 0.24 mmol, 1.00 equiv) and dichloromethane (10 mL). TEA (120 mg) was added dropwise at 0°C. tert-Butyl N-[1-(chlorosulfonyl)piperidin-4-yl]carbamate (350 mg, 1.17 mmol, 4.85 equiv) was then added in several portions. The resulting solution was stirred for 2 h at room temperature. The mixture was then concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (1/1). This resulted in 70 mg (56%) of tert-butyl N-[1-[(2S,4R)-4-(5-ethyl-1,2-thiazole-3-carboxamido)-2-methylpiperidine-1-sulfonyl]piperidin-4-yl]carbamate as a yellow solid. LCMS (method C, ESI): RT =1.54 min, m/z = 538.2 $[M+Na]^+$.

Step 4: Synthesis of N-((2S,4S)-1-(4-aminopiperidin-1-ylsulfonyl)-2-methylpiperidin-4-yl)-5-ethyl-1,2-thiazole-3-carboxamide

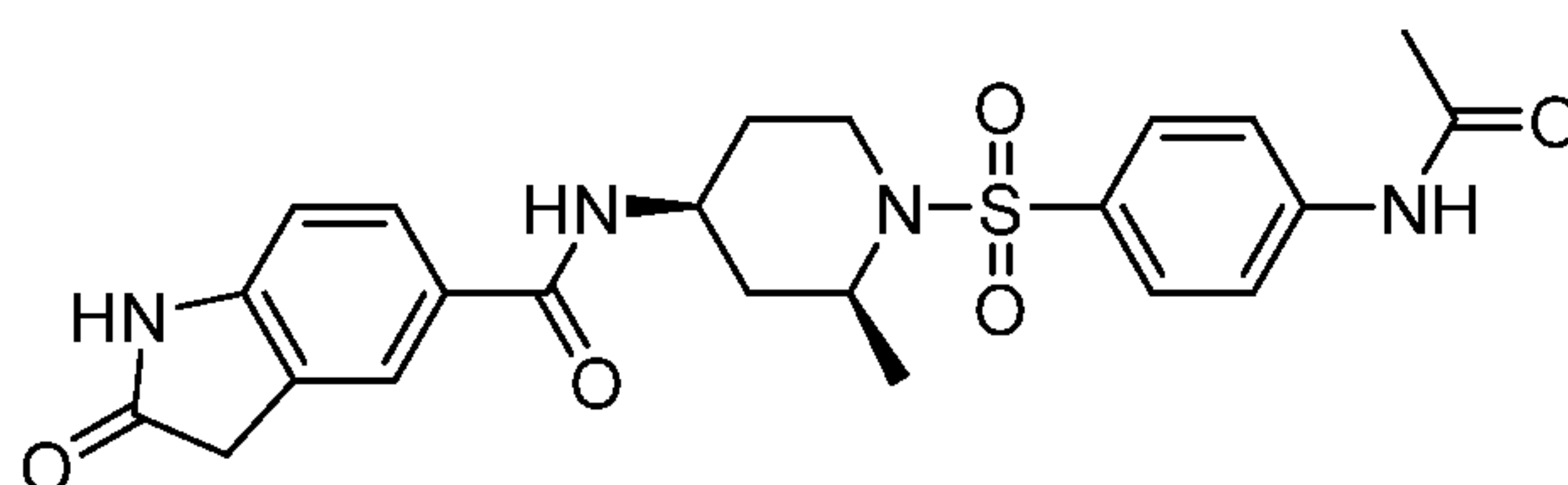


[0334] Into a 25-mL round-bottom flask was placed tert-butyl N-[1-[(2S,4R)-4-(5-ethyl-1,2-thiazole-3-carboxamido)-2-methylpiperidine-1-sulfonyl]piperidin-4-yl]carbamate (70 mg, 0.14 mmol, 1.00 equiv) and dichloromethane (10 mL). To the above hydrogen chloride (gas) was introduced. The resulting solution was stirred for 1 h at room temperature. The mixture was then concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: Column: X Bridge RP, 19*150 mm, 5 um; Mobile Phase A: Water/0.05% NH_4HCO_3 , Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 25%B to 45%B in 8 min; 254nm. This resulted in 13.8 mg (24%) of N-[(2S,4R)-1-(4-aminopiperidine-1-sulfonyl)-2-methylpiperidin-4-yl]-5-ethyl-1,2-thiazole-3-carboxamide as a white solid. ^1H NMR (400 MHz, CD_3OD) δ : 7.57 (s, 1H), ,

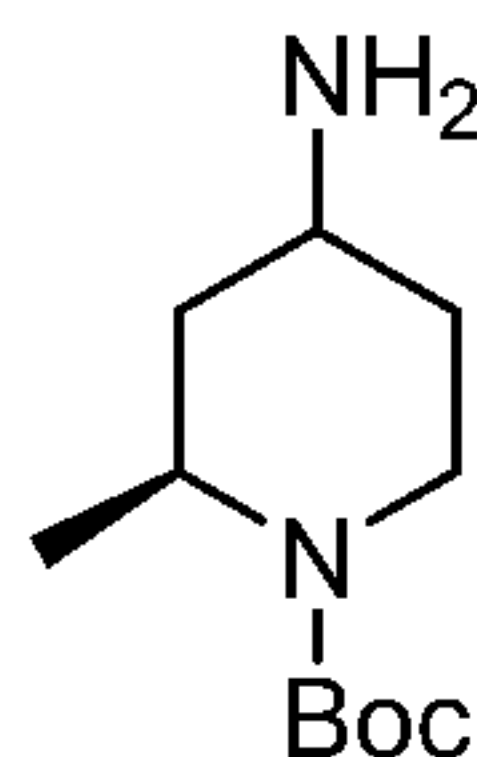
4.40-4.25 (m, 1H), 4.25-4.15 (m, 1H), 3.67-3.62 (m, 3H), 3.30-3.15 (m, 1H), 3.06-3.00 (m, 2H), 2.89-2.79 (m, 3H), 1.98-1.85 (m, 5H), 1.80-1.58 (m, 2H), 1.51-1.40 (m, 1H), 1.40-1.36 (m, 6H) *ppm*. LCMS (method A, ESI): RT = 1.68 min, m/z = 438.1 $[M+Na]^+$.

EXAMPLE 21

Synthesis of N-((2S,4S)-1-(4-acetamidophenylsulfonyl)-2-methylpiperidin-4-yl)-2-oxoindoline-5-carboxamide (Cpd. No. 632)

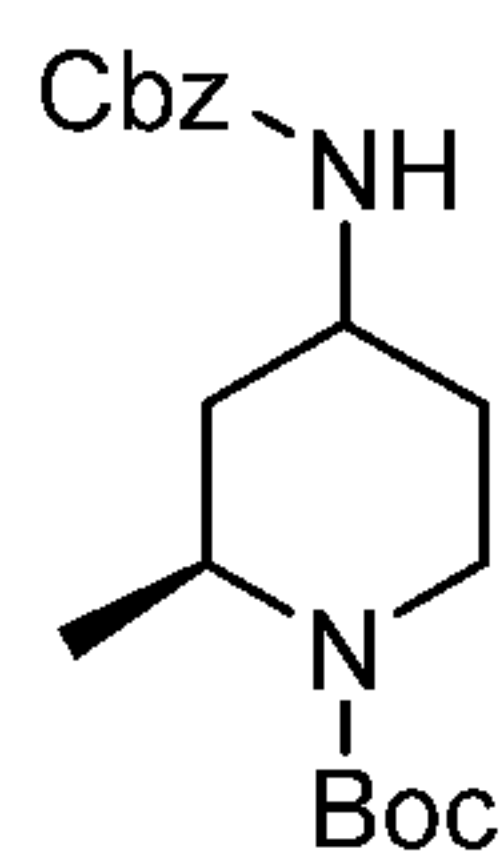


Step 1: Synthesis of (2S)-tert-butyl 4-amino-2-methylpiperidine-1-carboxylate



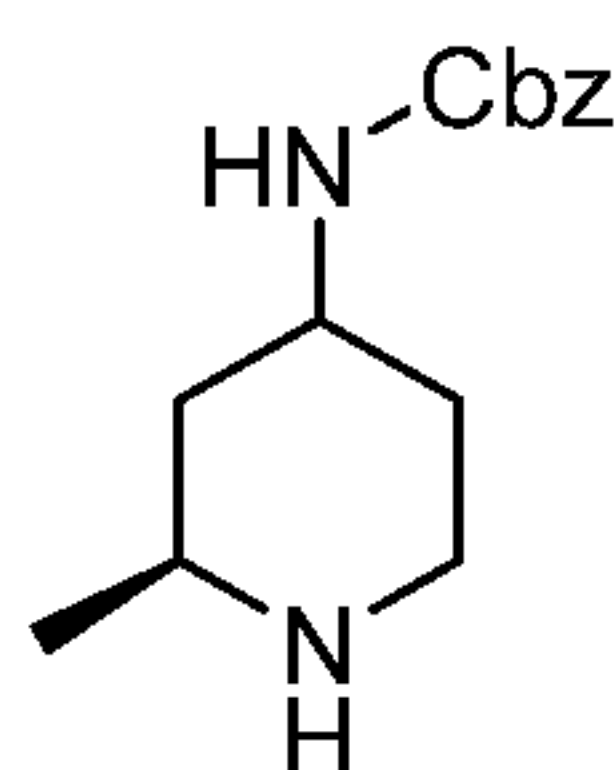
[0335] Into a 1-L round-bottom flask was placed methanol (600 mL), $HCOONH_4$ (32 g, 507.45 mmol, 36.08 equiv) and tert-butyl (2S)-2-methyl-4-oxopiperidine-1-carboxylate (3 g, 14.07 mmol, 1.00 equiv). $NaCNBH_3$ (1.7 g, 27.05 mmol, 1.92 equiv) was added batchwise slowly at 0-5°C. The resulting solution was stirred for 16 hours at 25°C. The reaction mixture was then diluted with 250 mL of ethyl acetate and washed with 3x250 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 2.5 g (83%) of tert-butyl (2S)-4-amino-2-methylpiperidine-1-carboxylate as colorless oil. ^1H -NMR (400 MHz, $CDCl_3$) δ : 4.13-4.11 (m, 1H), 3.98-3.97 (m, 1H), 3.49-3.28 (m, 2H), 2.24-2.10 (m, 2H), 1.76-1.75 (m, 2H), 1.45 (s, 9H), 1.27 (d, J = 6.0Hz, 3H) *ppm*. LCMS (method D, ESI): RT = 1.04 min, m/z = 215.0 $[M+H]^+$.

Step 2: Synthesis of (2S)-tert-butyl 4-(benzyloxycarbonylamino)-2-methylpiperidine-1-carboxylate



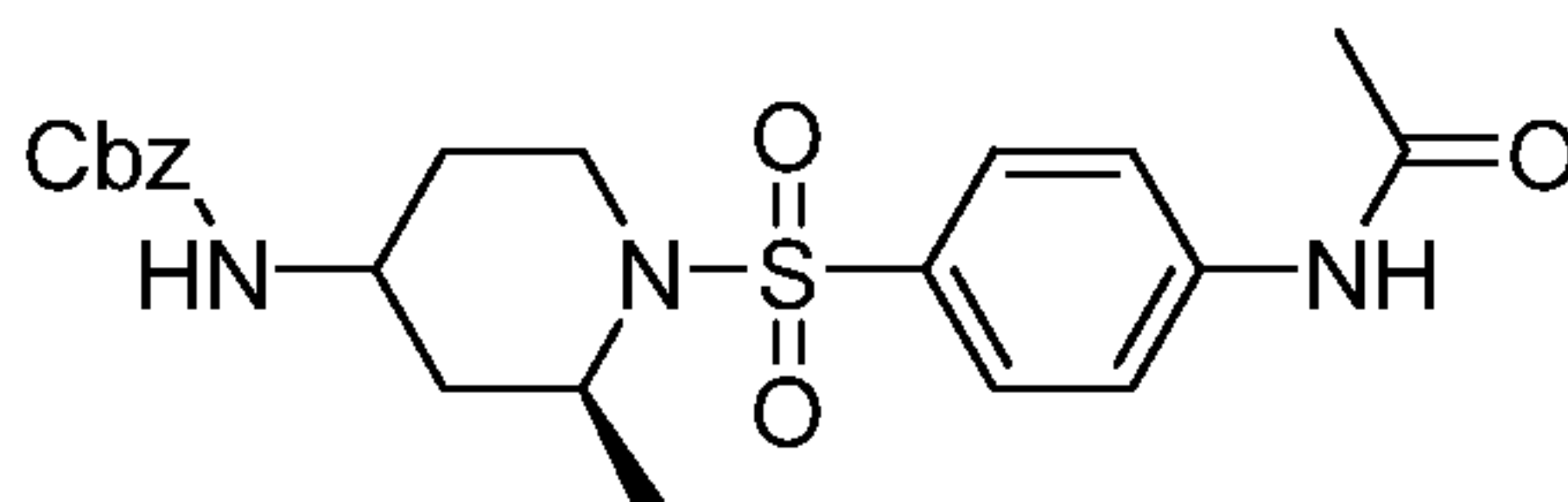
[0336] Into a 250-mL round-bottom flask was placed water (50 mL), tetrahydrofuran (50 mL), sodium carbonate (3.7 g, 34.91 mmol, 2.99 equiv), and tert-butyl (2S)-4-amino-2-methylpiperidine-1-carboxylate (2.5 g, 11.67 mmol, 1.00 equiv). Then benzyl chloroformate (4 g, 23.45 mmol, 2.01 equiv) was added dropwise at 0-5°C. The resulting solution was stirred for 16 hours at 25°C. The resulting mixture was concentrated under vacuum. The residue was diluted with 100 mL of ethyl acetate and washed with 3x100 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (1/1). This resulted in 2 g (49%) of tert-butyl (2S)-4-[[benzyloxy]carbonyl]amino]-2-methylpiperidine-1-carboxylate as colorless oil. ¹H-NMR (300 MHz, CD₃OD) δ : 7.36-7.30 (m, 5H), 5.09 (s, 2H), 4.10-4.08 (m, 1H), 3.76-3.70 (m, 2H), 3.27-3.17 (m, 1H), 1.97-1.78 (m, 3H), 1.62-1.55 (m, 1H), 1.41(s, 9H), 1.25 (d, *J*= 8.0Hz, 3H) *ppm*. LCMS (method D, ESI): RT = 1.57 min, *m/z* = 349.3 [M+H]⁺.

Step 3: Synthesis of Benzyl (2S)-2-methylpiperidin-4-ylcarbamate



[0337] Into a 25-mL round-bottom flask was placed tert-butyl (2S)-4-[[benzyloxy]carbonyl]amino]-2-methylpiperidine-1-carboxylate (400 mg, 1.15 mmol, 1.00 equiv) and dichloromethane (6 mL). Trifluoroacetic acid (3 mL) was then added dropwise at 0-5°C. The resulting solution was stirred for 30 min at 25°C. The mixture was concentrated under vacuum which resulted in 300 mg (crude) of benzyl N-[(2S)-2-methylpiperidin-4-yl]carbamate as a yellow liquid. LCMS (method A, ESI): RT =1.07 min, *m/z* = 249.1 [M+H]⁺.

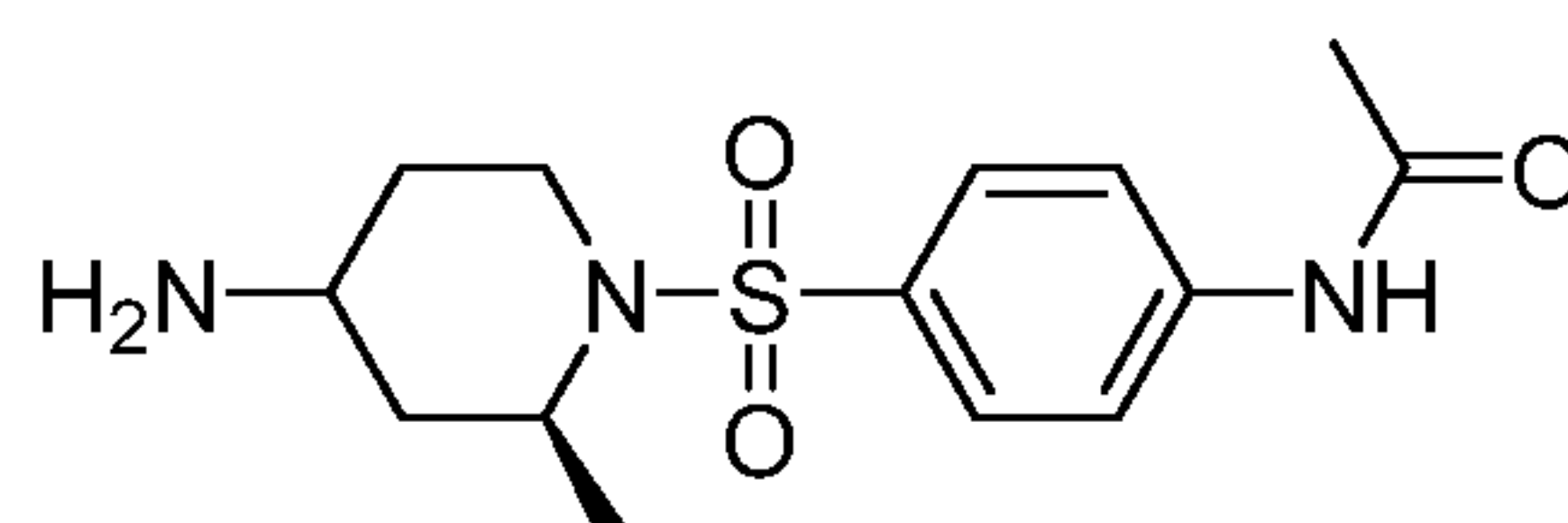
Step 4: Synthesis of benzyl (2S)-1-(4-acetamidophenylsulfonyl)-2-methylpiperidin-4-ylcarbamate



[0338] Into a 50-mL round-bottom flask was placed benzyl N-[(2S)-2-methylpiperidin-4-yl]carbamate (300 mg, 1.21 mmol, 1.00 equiv) and triethylamine (600 mg, 5.93 mmol, 4.00 equiv) in dichloromethane (30 mL). This was followed by the addition of 4-

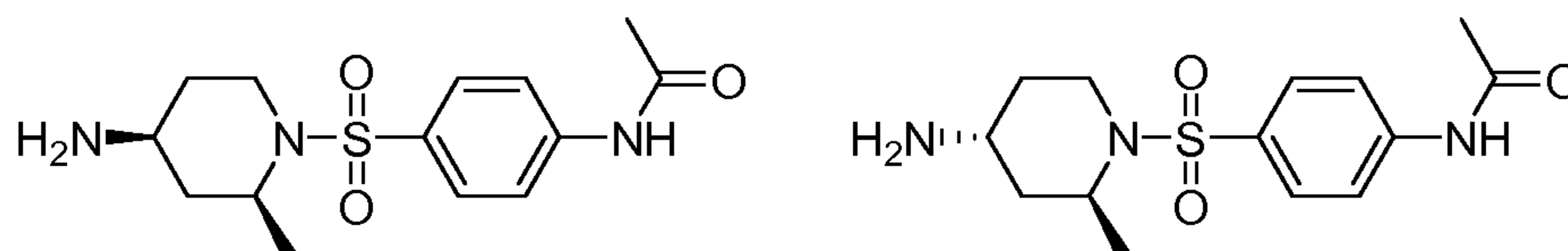
acetamidobenzene-1-sulfonyl chloride (720 mg, 3.08 mmol, 2.00 equiv) dropwise with stirring at 0°C. The resulting solution was stirred for 16 hours at 25°C. The mixture was then concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (2/1). This resulted in 300 mg (56%) of benzyl N-[(2S)-1-[(4-acetamidobenzene)sulfonyl]-2-methylpiperidin-4-yl]carbamate as a yellow solid. LCMS (method D, ESI): RT = 1.40 min, m/z = 446.2 [M+H]⁺.

Step 5: Synthesis of N-(4-((2S)-4-amino-2-methylpiperidin-1-ylsulfonyl)phenyl)acetamide



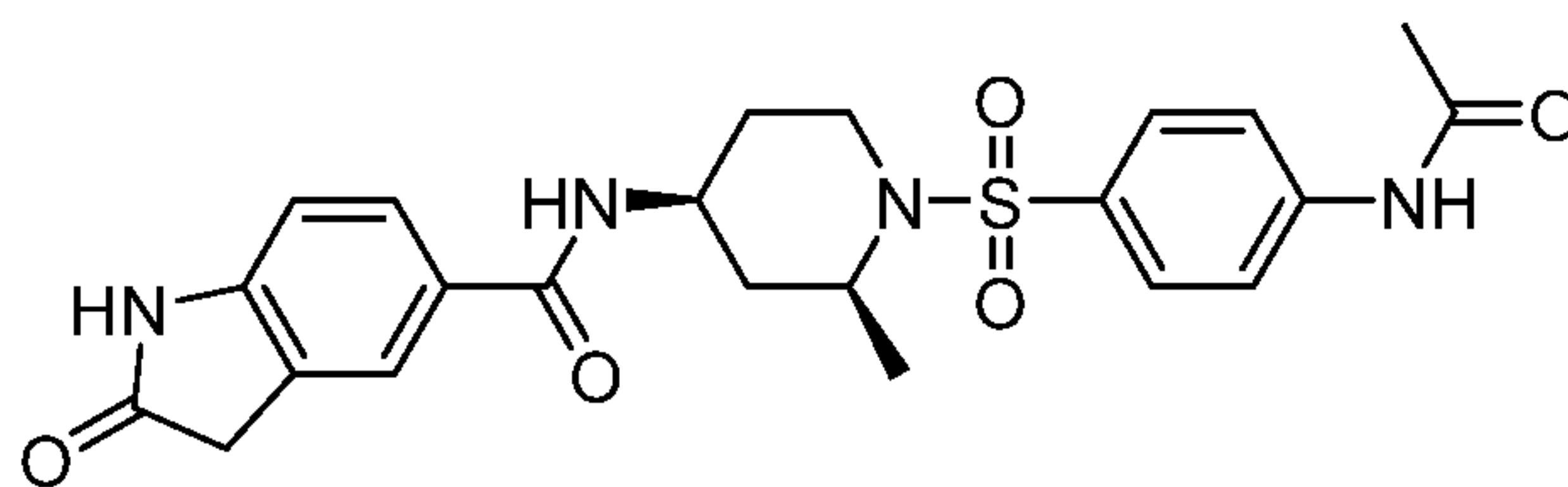
Into a 50-mL round-bottom flask was placed benzyl N-[(2S)-1-[(4-acetamidobenzene)sulfonyl]-2-methylpiperidin-4-yl]carbamate (300 mg, 0.67 mmol, 1.00 equiv) and trifluoroacetic acid (10 mL). The resulting solution was stirred for 1 hour at 60°C in an oil bath. The mixture was then concentrated under vacuum. This resulted in 280 mg (crude) of N-[4-[(2S)-4-amino-2-methylpiperidine-1-sulfonyl]phenyl]acetamide as yellow oil. LCMS (method D, ESI): RT = 0.96 min, m/z = 312.2 [M+H]⁺.

Step 6: Synthesis of N-(4-((2S,4S)-4-amino-2-methylpiperidin-1-ylsulfonyl)phenyl)acetamide and N-(4-(((2S,4R)-4-amino-2-methylpiperidin-1-yl)sulfonyl)phenyl)acetamide



[0339] N-[4-[(2S)-4-amino-2-methylpiperidine-1-sulfonyl]phenyl]acetamide (200 mg, 0.64 mmol, 1.00 equiv) was separated by Prep-SFC with the following conditions: Column, Lux 5u Cellulose-44.6*150mm, 5um Chiral-A(LUX-4); mobile phase, 25% IPA with MeOH; Detector, UV 254/220 nm. This resulted in 100 mg (100%) of N-[4-[(2S,4S)-4-amino-2-methylpiperidine-1-sulfonyl]phenyl]acetamide as a yellow solid and 40 mg (98%) of N-[4-[(2S,4R)-4-amino-2-methylpiperidine-1-sulfonyl]phenyl]acetamide as a yellow solid. ee value: 100%.

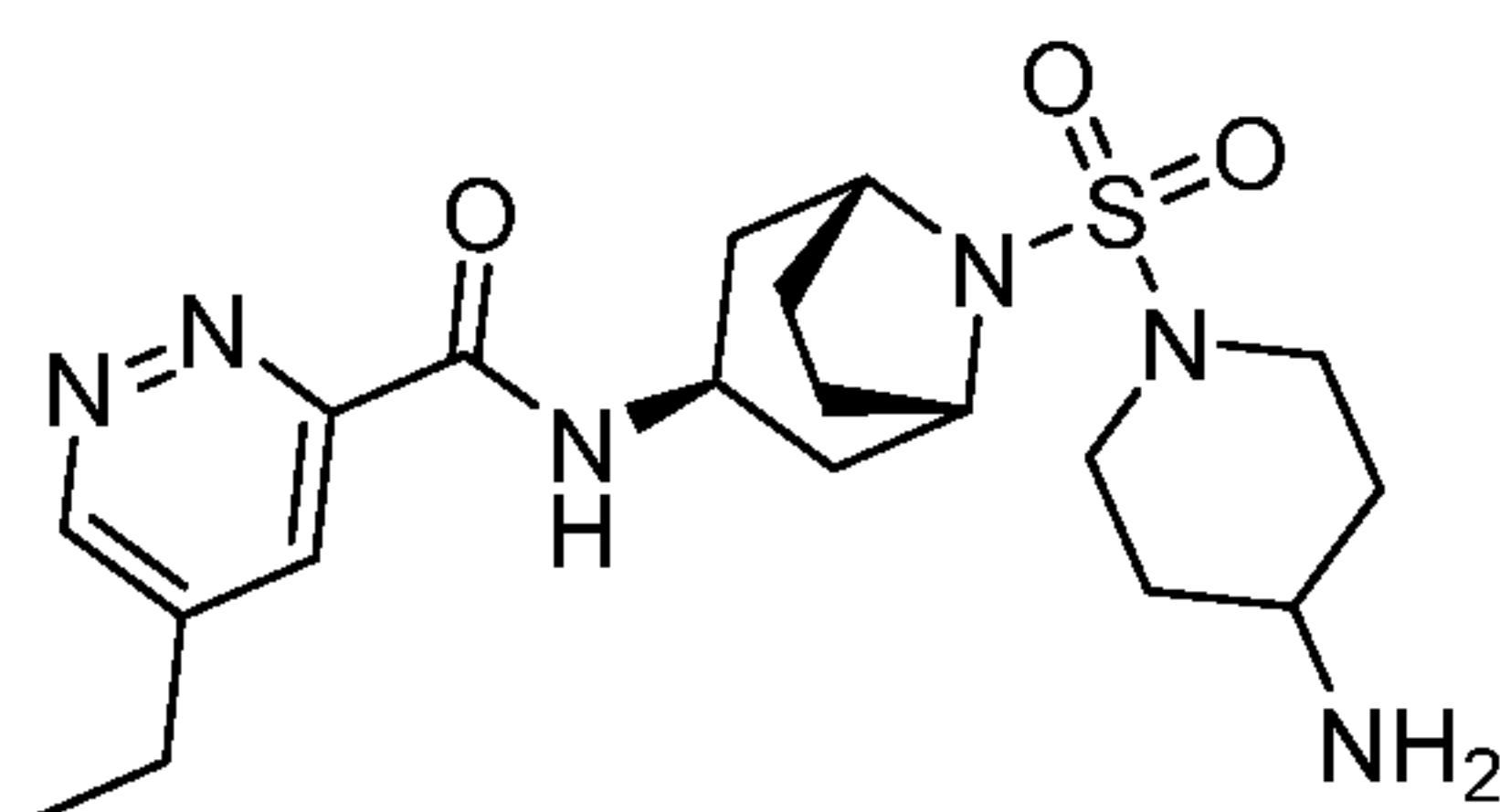
Step 7: Synthesis of N-((2S,4S)-1-(4-acetamidophenylsulfonyl)-2-methylpiperidin-4-yl)-2-oxoindoline-5-carboxamide



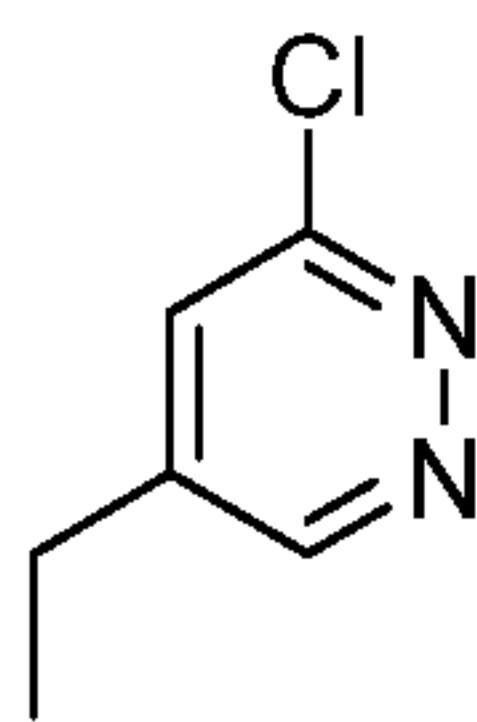
[0340] Into a 10-mL round-bottom flask was placed 2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid (48 mg, 0.27 mmol, 2.00 equiv), 1-hydroxybenzotriazole (40 mg, 1.26 mmol, 2.00 equiv), triethylamine (50 mg, 0.49 mmol, 4.00 equiv), N-[4-[(2S,4S)-4-amino-2-methylpiperidine-1-sulfonyl]phenyl]acetamide (40 mg, 0.13 mmol, 1.00 equiv), and dichloromethane (4 mL). N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (56 mg, 0.29 mmol, 2.00 equiv) was added batchwise at 0-5°C. The resulting solution was stirred for 16 hours at 25°C. The mixture was then washed with 3x5 mL of brine and the organic layer concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (2#-Waters 2767-2(HPLC-08)): Column, Xbridge Shield RP 18, 5um, 19*150mm; mobile phase, water with 50mmol NH₄HCO₃ and CH₃CN (10.0% CH₃CN up to 28.0% in 2 min, up to 46.0% in 10 min, up to 100.0% in 1 min, down to 10.0% in 1 min); Detector, UV 254 nm. This resulted in 2.6 mg (4%) of N-[(2S,4S)-1-[(4-acetamidobenzene)sulfonyl]-2-methylpiperidin-4-yl]-2-oxo-2,3-dihydro-1H-indole-5-carboxamide as a white solid. ¹H-NMR (400 MHz, CD₃OD) δ : 7.84-7.78 (m, 4H), 7.74-7.71 (m, 2H), 6.95 (d, *J*=8.0Hz, 1H), 3.95-3.90 (m, 2H), 3.62-3.51(m, 1H), 3.33-3.32 (m, 2H), 3.15-3.04 (m, 1H), 2.19 (s, 3H), 2.06-1.98 (m, 1H), 1.93-1.88 (m, 1H), 1.73-1.68 (m, 2H), 1.40 (d, *J*=8.0Hz, 3H) ppm. LCMS (method D, ESI): RT = 2.62 min, *m/z* = 471.2 [M+H]⁺.

EXAMPLE 22

Synthesis of N-[(1R,3r,5S)-8-(4-aminopiperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-5-ethylpyridazine-3-carboxamide trifluoroacetate (Cpd. No. 616)

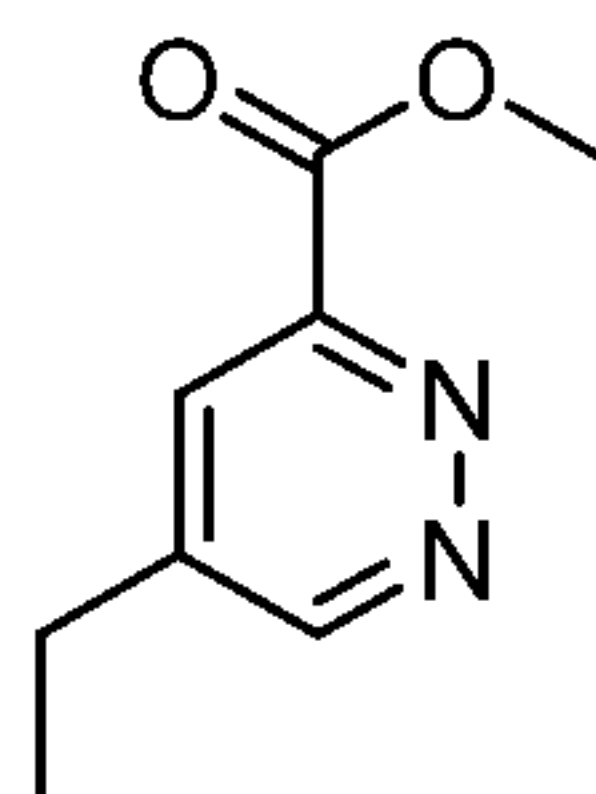


Step 1: Synthesis of 3-chloro-5-ethylpyridazine



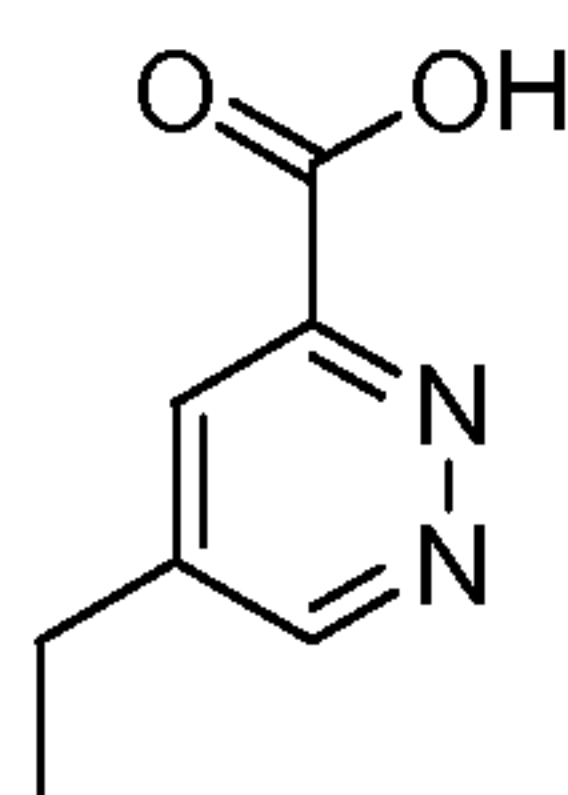
[0341] Into a 50-mL round-bottom flask was placed 5-ethyl-2,3-dihydropyridazin-3-one (100 mg, 0.81 mmol, 1.00 equiv) and POCl_3 (5 mL). The resulting solution was stirred for 2 hours at 80°C in an oil bath. The mixture was then concentrated under vacuum. The residue was extracted with 1 x100 mL of dichloromethane and the organic layer washed with 50 mL of sodium bicarbonate (aq. sat.) and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (30:100). This resulted in 80 mg (69%) of 3-chloro-5-ethylpyridazine as yellow oil. TLC, $R_f = 0.2$ (PE:EA=10:1).

Step 2: Synthesis of methyl 5-ethylpyridazine-3-carboxylate



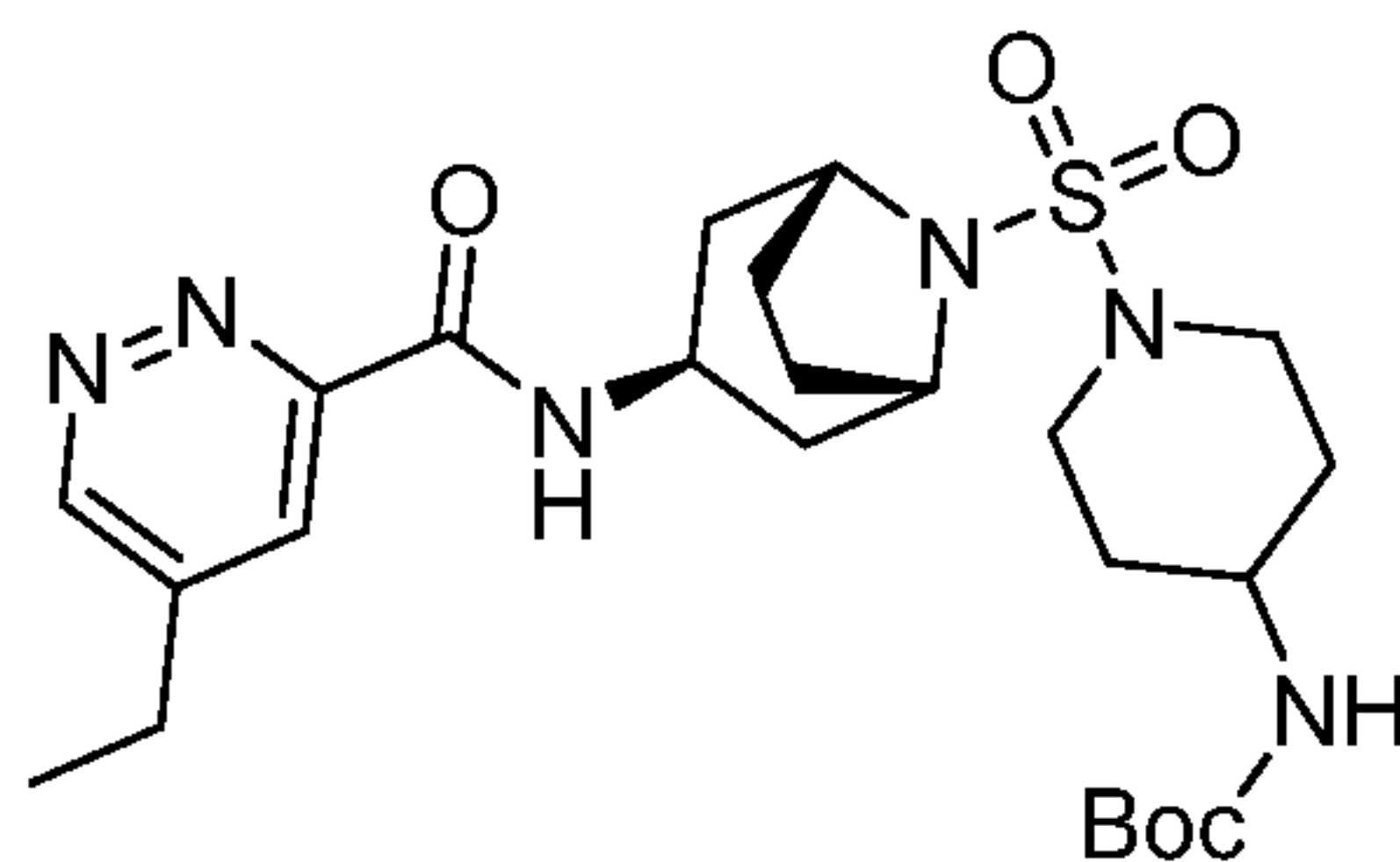
[0342] Into a 30-mL pressure tank reactor (100 mL) was placed 3-chloro-5-ethylpyridazine (80 mg, 0.55 mmol, 1.00 equiv), methanol (10 mL), triethylamine (112 mg, 1.11 mmol, 2.02 equiv), and Pd(dppf)Cl_2 (148 mg). To the above CO (gas) was introduced and maintained at 30 atm. The resulting solution was stirred for 15 h at 80°C . The solids were filtered out. The filtrate was extracted with 2x100 mL of ethyl acetate and the organic layers combined, washed with 50 mL of brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (30:100). This resulted in 80 mg (86%) of methyl 5-ethylpyridazine-3-carboxylate as yellow oil. LCMS (method C, ESI): $\text{RT} = 0.78$ min, $m/z = 167.0$ $[\text{M}+\text{H}]^+$.

Step 3: Synthesis of 5-ethylpyridazine-3-carboxylic acid



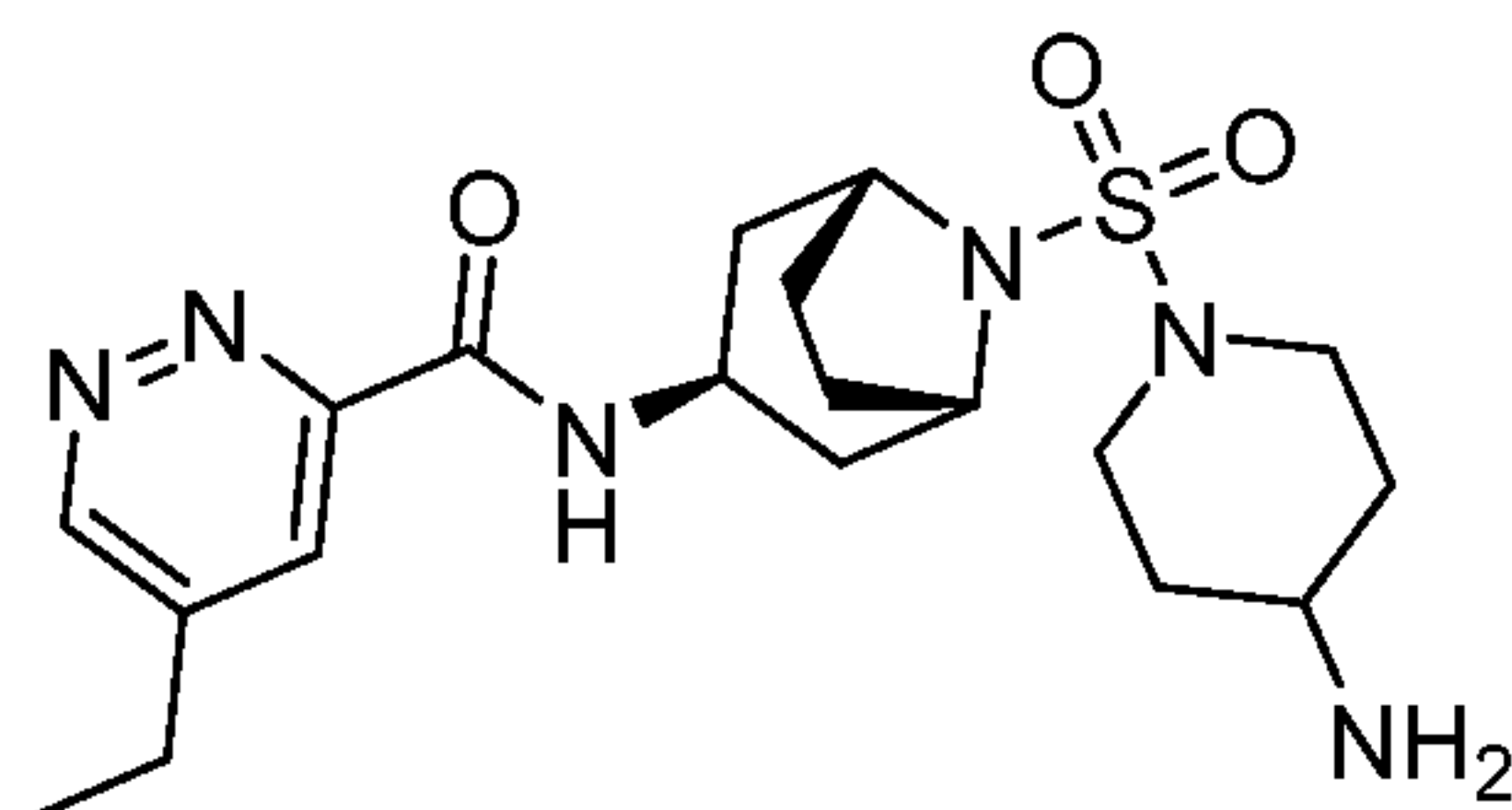
[0343] Into a 10-mL round-bottom flask was placed methyl 5-ethylpyridazine-3-carboxylate 80 mg, 0.48 mmol, 1.00 equiv) and C₂H₅OH (5 mL). This was followed by the addition of a solution of LiOH.H₂O (100 mg, 2.4 mmol, 5.00 equiv) in water (1 mL) which was added dropwise with stirring at 0°C. The resulting solution was stirred for 3 hour at 20°C. The reaction was then quenched by the addition of 50 mL of water. The pH was adjusted to 5 with hydrochloric acid (6N). The mixture was extracted with 2x100 mL of dichloromethane and the combined organic layers dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 60 mg (34.7%) of 5-ethylpyridazine-3-carboxylic acid as black oil. LCMS (method D, ESI): RT = 0.90 min, m/z = 153.0 [M+H]⁺.

Step 4: Synthesis of tert-butyl N-[1-[(1R,3r,5S)-3-(5-ethylpyridazine-3-carboxamido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate



[0344] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed dichloromethane 20 mL) and 5-ethylpyridazine-3-carboxylic acid (60 mg, 0.39 mmol, 1.00 equiv). To the above was added tert-butyl N-[1-[(1R,3r,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate (150 mg, 0.39 mmol, 0.98 equiv), HOBt (79 mg, 0.58 mmol, 1.49 equiv), and EDCI (223 mg, 1.17 mmol, 2.99 equiv). This was followed by the addition of a solution of triethylamine (118 mg, 1.17 mmol, 2.99 equiv) in dichloromethane (2 mL) which was added dropwise with stirring at 0°C over 3 min. The resulting solution was stirred for 15 hours at 20°C. The mixture was extracted with 2x100 mL of dichloromethane and the organic layers combined, washed with 50 mL of water and 50 mL of brine, and concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (50:100). This resulted in 50 mg (24%) of tert-butyl N-[1-[(1R,3r,5S)-3-(5-ethylpyridazine-3-carboxamido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate as yellow oil. LCMS (method D, ESI): RT = 1.46 min, m/z = 523.0 [M+H]⁺.

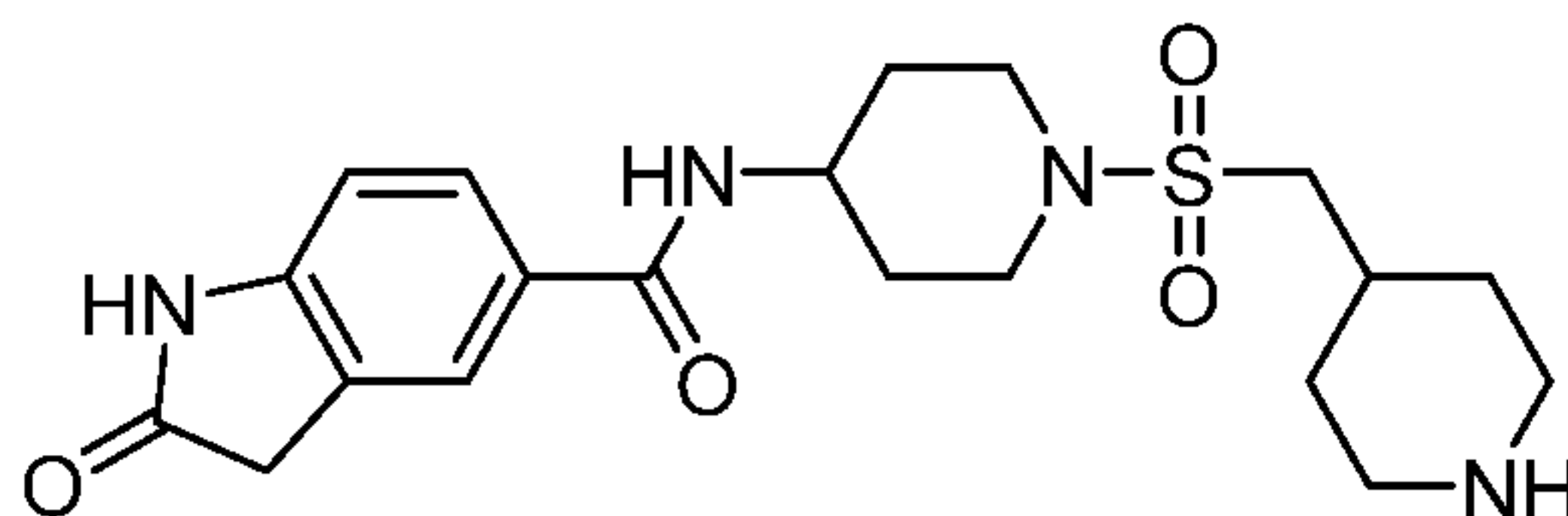
Step 5: Synthesis of N-[(1R,3r,5S)-8-(4-aminopiperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-5-ethylpyridazine-3-carboxamide trifluoroacetate



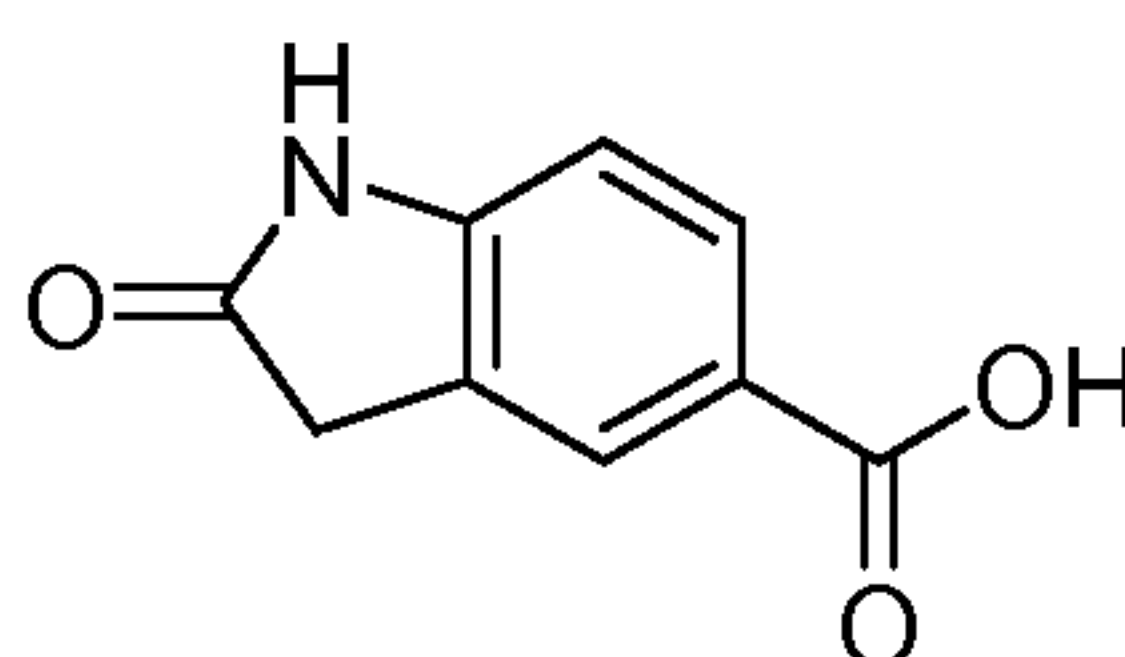
[0345] Into a 25-mL round-bottom flask was placed tert-butyl N-[1-[(1R,3r,5S)-3-(5-ethylpyridazine-3-carboxamido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate (50 mg, 0.10 mmol, 1.00 equiv) and hydrogen chloride/dioxane (10 mL, saturated, this solution was made by introducing hydrogen chloride gas into 1,4-dioxane under 0°C for 6 hours). The resulting solution was stirred for 4 h at 20°C. The mixture was then concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: Column: X Select C18, 19*250 mm, 5 μ m; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 12% B to 52% B in 11.5 min; 254nm. This resulted in 17.9 mg (35%) of N-[(1R,3r,5S)-8-(4-aminopiperidine-1-sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-5-ethylpyridazine-3-carboxamide trifluoroacetate as a yellow solid. ^1H NMR (300 MHz, CD_3OD) δ : 9.29 (s, 1H), 8.19 (s, 1H), 4.37-4.28 (m, 1H), 4.21-4.11 (s, 2H), 3.86 (d, $J=15.0\text{Hz}$, 2H), 3.30-3.20 (m, 1H), 2.99-2.80 (m, 4H), 2.45-2.30 (m, 2H), 2.18-2.00 (m, 8H), 1.79-1.61 (m, 2H), 1.40-1.29 (m, 3H) ppm. LCMS (method D, ESI): RT =1.27 min, m/z = 423.2 $[\text{M}+\text{H}]^+$.

EXAMPLE 23

Synthesis of 2-oxo-N-[1-[(piperidin-4-ylmethane)sulfonyl]piperidin-4-yl]-2,3-dihydro-1H-indole-5-carboxamide trifluoroacetate (Cpd. No. 620)

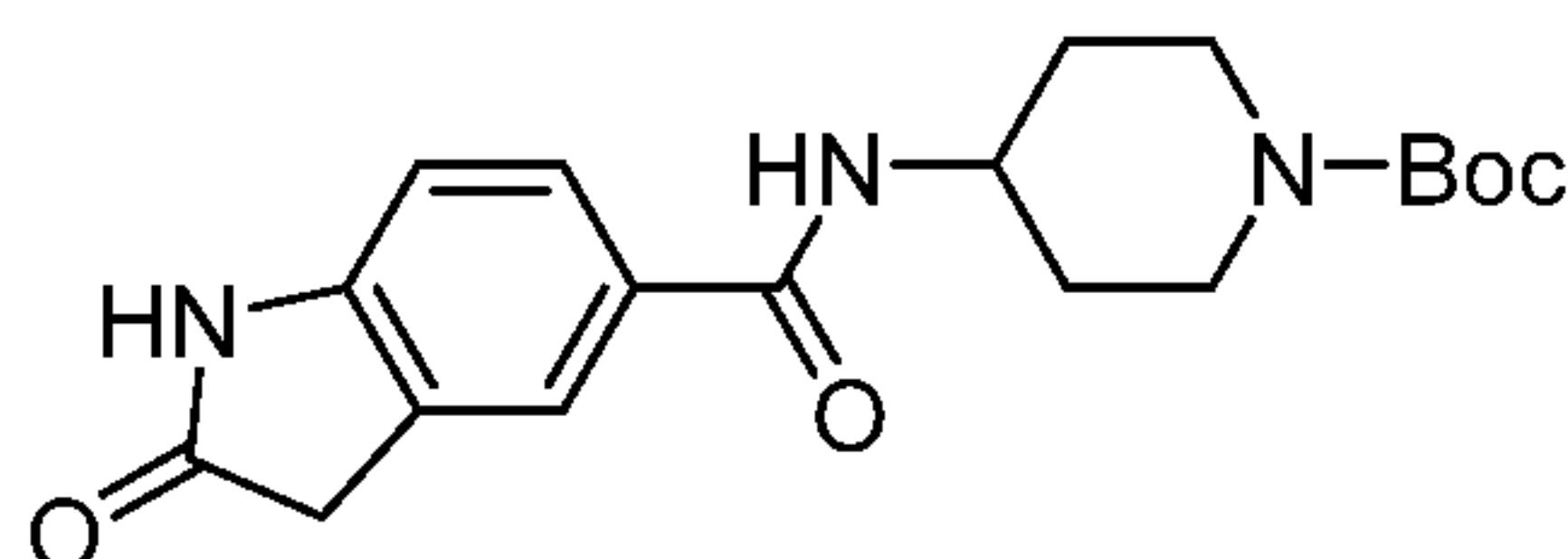


Step 1: Synthesis of 2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid



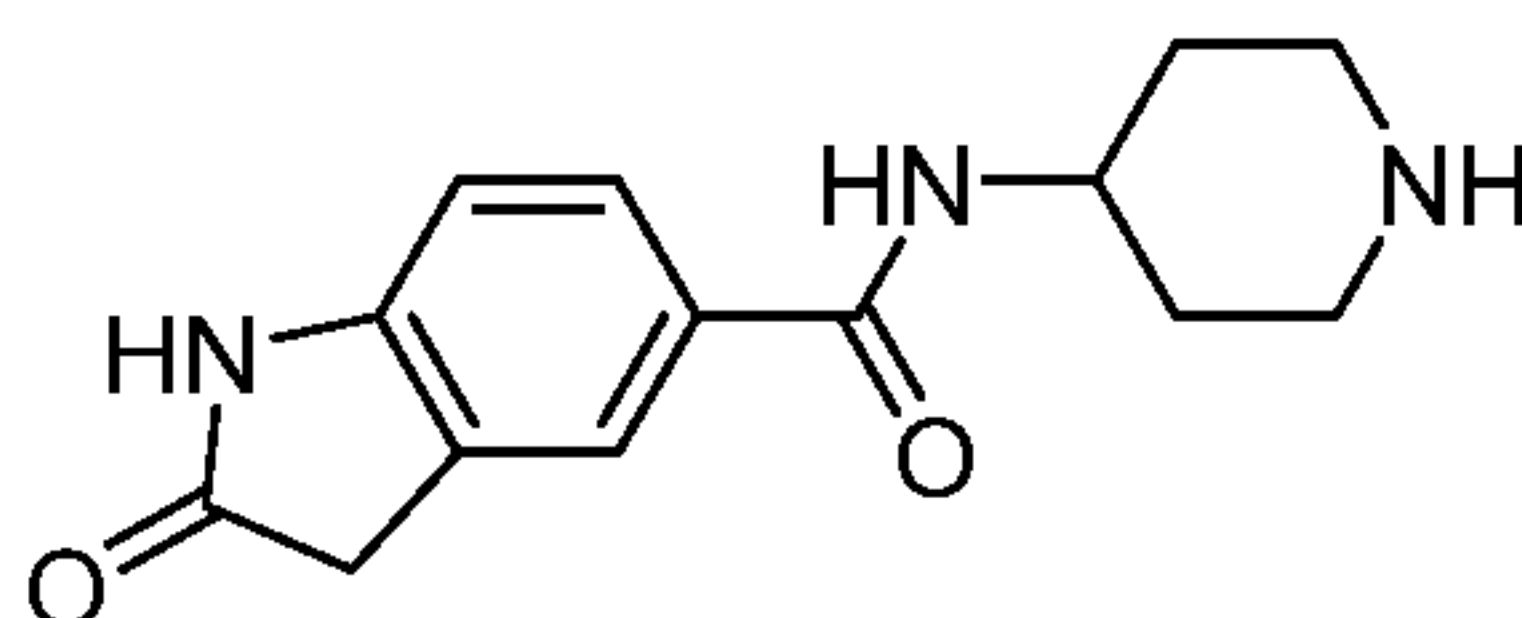
[0346] Into a 50-mL round-bottom flask was placed methyl 2-oxo-2,3-dihydro-1H-indole-5-carboxylate (800 mg, 4.18 mmol, 1.00 equiv) and methanol (10 mL). This was followed by the addition of a solution of NaOH (670 mg, 16.75 mmol, 4.00 equiv) in water (10 mL) dropwise with stirring at 0°C. The resulting solution was stirred for 14 h at 20°C. The mixture was then concentrated under vacuum and the residue taken up in 20 mL of H₂O. This was washed with 2x5 mL of dichloromethane. The pH was adjusted to 4 with hydrochloric acid (1 N) and extracted with 5x50 mL of ethyl acetate and the organic layers combined. Concentration resulted in 592 mg (80%) of 2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid as a yellow solid. ¹H NMR (400 MHz, DMSO) δ : 12.5 (brs, 1H), 10.7 (s, 1H), 7.82 (d, *J*=8.4Hz, 1H), 7.76 (s, 1H), 6.88 (d, *J*=8.0Hz, 1H), 3.54 (s, 2H) ppm. LCMS (method A, ESI): RT = 0.97 min, *m/z* = 178.0 [M+H]⁺.

Step 2: Synthesis of tert-butyl 4-(2-oxo-2,3-dihydro-1H-indole-5-carboxamido)piperidine-1-carboxylate



[0347] Into a 25-mL round-bottom flask was placed tert-butyl 4-aminopiperidine-1-carboxylate (300 mg, 1.50 mmol, 1.00 equiv), dichloromethane (10 mL), 2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid (319 mg, 1.80 mmol, 1.20 equiv), EDCI (344 mg, 1.79 mmol, 1.20 equiv), and HOBt (304 mg, 2.25 mmol, 1.50 equiv). This was followed by the addition of TEA (454 mg, 4.49 mmol, 3.00 equiv) dropwise with stirring at 0°C. The resulting solution was stirred for 14 h at 20°C. The solids were collected by filtration. This resulted in 393 mg (73%) of tert-butyl 4-(2-oxo-2,3-dihydro-1H-indole-5-amido)piperidine-1-carboxylate as a yellow solid. LCMS (method C, ESI): RT = 0.78 min, *m/z* = 304.0 [M+H-56]⁺.

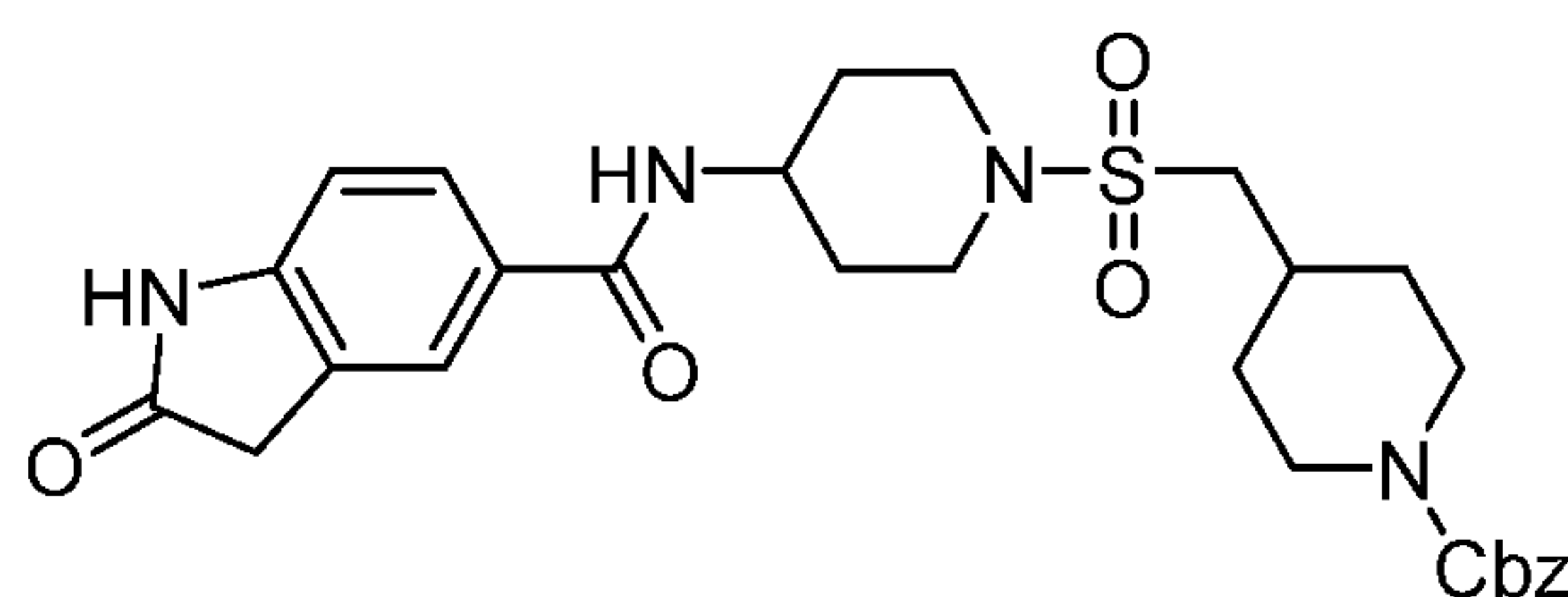
Step 3: Synthesis of 2-oxo-N-(piperidin-4-yl)-2,3-dihydro-1H-indole-5-carboxamide hydrochloride



[0348] Into a 25-mL round-bottom flask was placed tert-butyl 4-(2-oxo-2,3-dihydro-1H-indole-5-carboxamido)piperidine-1-carboxylate (250 mg, 0.70 mmol, 1.00 equiv) and hydrogen chloride/dioxane (3 mL, saturated, this solution was made by introducing

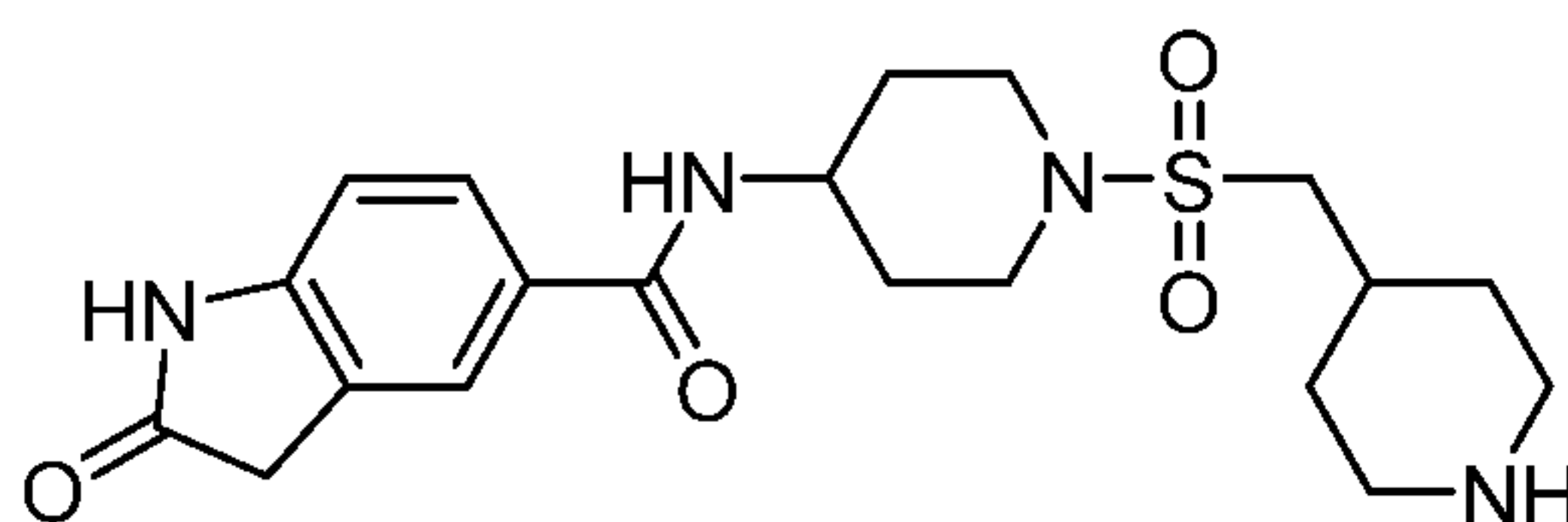
hydrogen chloride gas into 1,4-dioxane under 0°C for 6 hours). The resulting solution was stirred for 2 h at 20°C. The mixture was then concentrated under vacuum. This resulted in 200 mg (97%) of 2-oxo-N-(piperidin-4-yl)-2,3-dihydro-1H-indole-5-carboxamide hydrochloride as a light yellow solid. ¹H NMR (400 MHz, D₂O) δ : 7.65 (s, 2H), 6.95(s, 1H), 4.04 (t, *J*=10.4Hz, 1H), 3.54 (s, 2H), 3.42 (d, *J*=13.2Hz, 2H), 3.12-3.01 (m, 2H), 2.13 (d, *J*=14.0Hz, 2H), 1.81-1.65 (m, 2H) *ppm*. LCMS (method A, ESI): RT =0.89 min, *m/z* = 260.0 [M+H]⁺.

Step 4: Synthesis of benzyl 4-[[4-(2-oxo-2,3-dihydro-1H-indole-5-carboxamido)piperidine-1-sulfonyl]methyl]piperidine-1-carboxylate



[0349] Into a 50-mL round-bottom flask was placed 2-oxo-N-(piperidin-4-yl)-2,3-dihydro-1H-indole-5-carboxamide hydrochloride (80 mg, 0.27 mmol, 1.00 equiv) and NMP (16 mL). This was followed by the addition of TEA (82 mg, 0.81 mmol, 3.00 equiv) dropwise with stirring at 0°C. To this was then added benzyl 4-[(chlorosulfonyl)methyl]piperidine-1-carboxylate (135 mg, 0.41 mmol, 1.50 equiv) in several batches at 0°C. The resulting solution was stirred for 2 h at 20°C. The mixture was concentrated under vacuum. The residue was chromatographed on a silica gel column with dichloromethane/methanol (50:1-20:1). The collected fractions were combined and concentrated under vacuum. This resulted in 100 mg (67%) of benzyl 4-[[4-(2-oxo-2,3-dihydro-1H-indole-5-carboxamido)piperidine-1-sulfonyl]methyl]piperidine-1-carboxylate as a yellow solid. LCMS (method C, ESI): RT =1.04 min, *m/z* = 555.0 [M+H]⁺.

Step 5: Synthesis of 2-oxo-N-[1-[(piperidin-4-ylmethane)sulfonyl]piperidin-4-yl]-2,3-dihydro-1H-indole-5-carboxamide trifluoroacetate

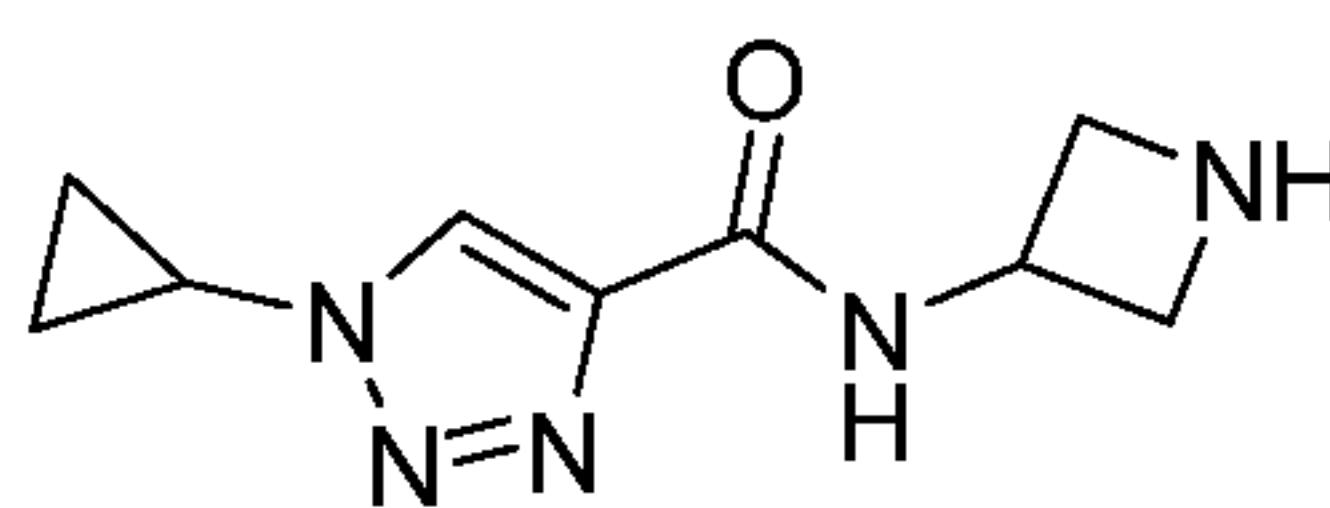


[0350] Into a 25-mL round-bottom flask was placed benzyl 4-[[4-(2-oxo-2,3-dihydro-1H-indole-5-carboxamido)piperidine-1-sulfonyl]methyl]piperidine-1-carboxylate (80 mg,

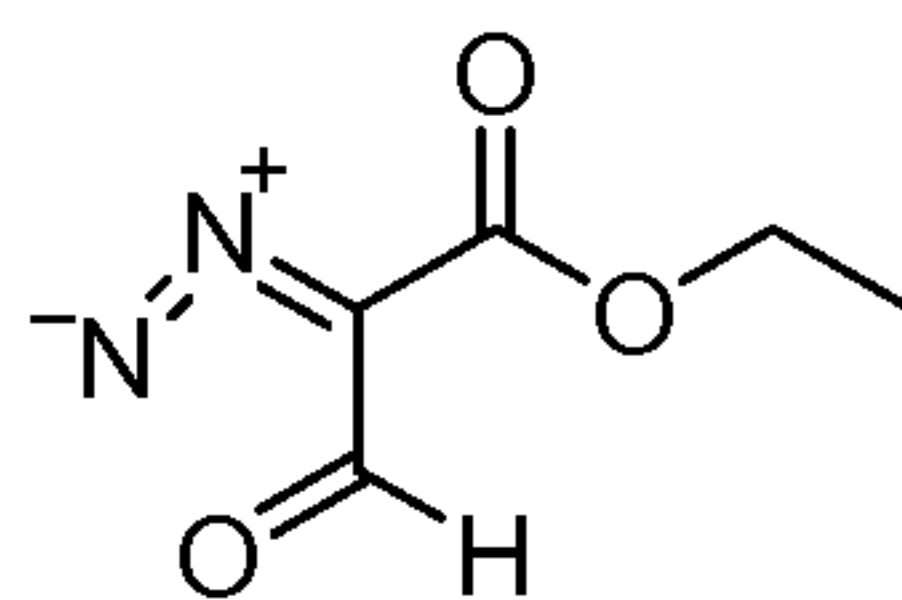
0.14 mmol, 1.00 equiv) and hydrochloric acid (12 N, 5 mL). The resulting solution was stirred for 2 h at 20°C. The mixture was then concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: Column: X Bridge C18, 19*150 mm, 5 μ m; Mobile Phase A: Water/0.05%TFA, Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 15%B to 43%B in 10 min; Detector: 254nm. This resulted in 13.2 mg (17%) of 2-oxo-N-[1-[(piperidin-4-ylmethane)sulfonyl]piperidin-4-yl]-2,3-dihydro-1H-indole-5-carboxamide trifluoroacetate as a white solid. ^1H NMR (400 MHz, D_2O) δ : 7.61 (s, 2H), 7.00 (d, $J=4.4\text{Hz}$, 1H), 4.00-3.90 (m, 1H), 3.75-3.66 (m, 2H), 3.60 (s, 2H), 3.43-3.37 (m, 2H), 3.15 (d, $J=6.4\text{Hz}$, 2H), 3.05-2.92 (m, 4H), 2.31-2.18 (m, 1H), 2.15-1.97 (m, 4H), 1.69-1.50 (m, 4H) *ppm*. LCMS (method A, ESI): RT =1.03 min, m/z = 421.1 $[\text{M}+\text{H}]^+$.

EXAMPLE 24

Synthesis of N-(azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide

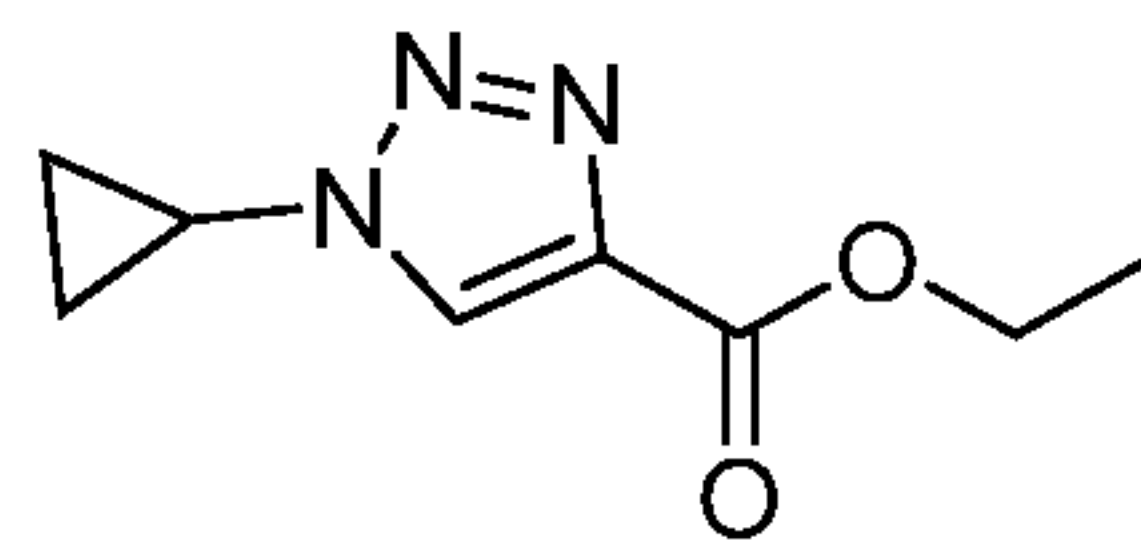


Step 1: Synthesis of Ethyl 2-diazo-3-oxopropanoate



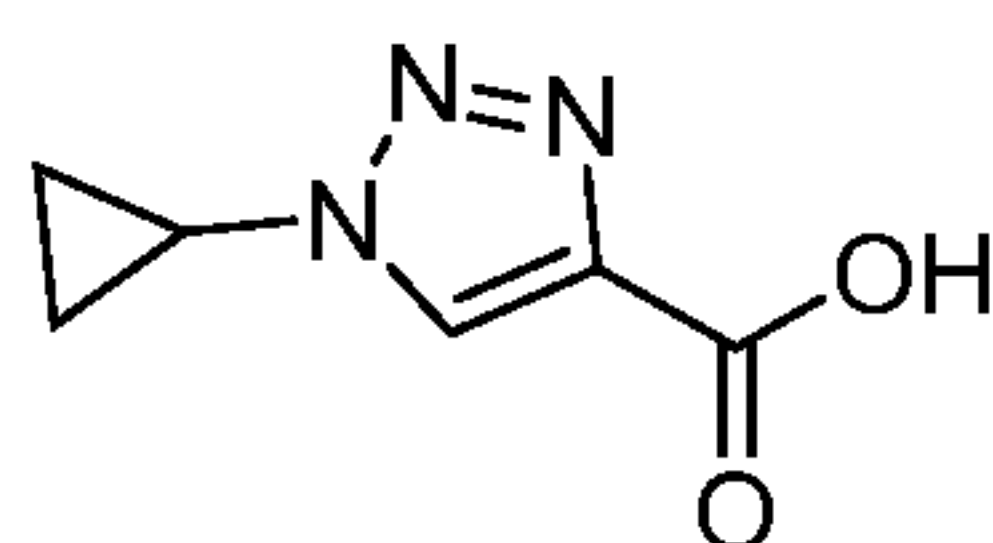
[0351] Oxalyl chloride (87.9 g, 693 mmol) was added to a cold solution of N,N-dimethylformamide (42.3 g, 578 mmol) in CHCl_3 (150 mL) and the reaction was stirred at room temperature for 30 min, followed by heating at 40 °C for a further 1h. After chilling the reaction to -10 °C, ethyl 2-diazoacetate (63.0 g, 552 mmol) was added and the mixture was stirred at room temperature for 2h. The mixture was then concentrated and the residue was diluted with ether(200 mL), the solid was collected by filtration and dissolved in 10% aq. HOAc(200 mL), then stirred for a further 1h. The resulting mixture was extracted with ethyl acetate (300 mL x3) and the organic was washed with saturated Na_2CO_3 aq.(300 mL) and brine (300 mL), dried over Na_2SO_4 , filtered and concentrated to give crude ethyl 2-diazo-3-oxopropanoate (27 g, 32.8 %) as red oil , which was used for next step without further purification. ^1H -NMR (400 MHz, CD_3OD) δ ppm: 9.67 (s, 1H), 4.33 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.2, 3H).

Step 2: Synthesis of ethyl 1-cyclopropyl-1H-1,2,3-triazole-4-carboxylate



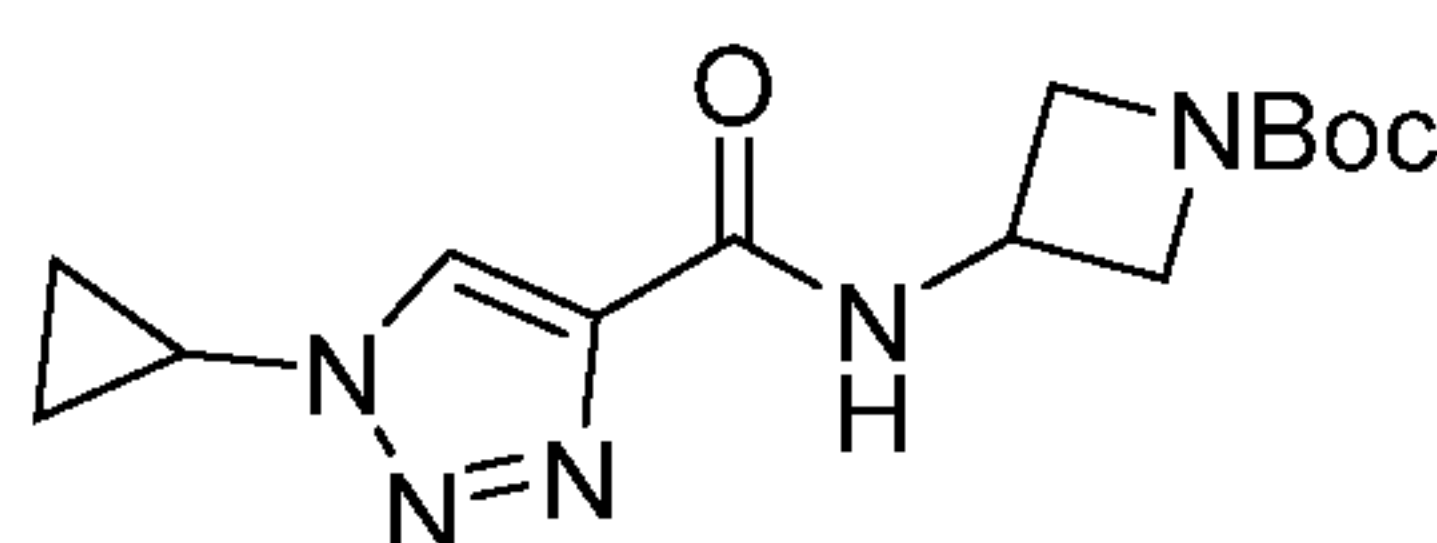
[0352] To a solution of ethyl 2-diazo-3-oxopropanoate (27 g, 189 mmol) in EtOH (100 mL) was added acetic acid (28.3 g, 472 mmol). Cyclopropanamine (10.7 g, 189 mmol) was added slowly and the mixture was stirred at room temperature overnight. The solvent was removed and saturated Na_2CO_3 aq. was added to the residue to bring the pH to 8. The mixture was extracted with ethyl acetate (200 mL x3), washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated. The resulting residue was purified by flash chromatography (PE:EA=2:1) to give crude ethyl 1-cyclopropyl-1H-1,2,3-triazole-4-carboxylate (18.5 g, 54.0 %) as yellow oil. ESI-LCMS (m/z): 182.2 $[\text{M}+\text{H}]^+$.

Step 3: Synthesis of 1-cyclopropyl-1H-1,2,3-triazole-4-carboxylic acid



[0353] To a solution of ethyl 1-cyclopropyl-1H-1,2,3-triazole-4-carboxylate (18.5 g, 102 mmol) in THF (80 mL)/ H_2O (40 mL) was added lithium hydroxide hydrate (4.5 g, 107 mmol), the resulting mixture was stirred at room temperature for 3hr. The solvent was removed and the residue was dissolved in H_2O (50 mL), extracted with EA (100 mL). The organic phase was discarded and the water phase was acidified with 2N HCl until the pH = 5, The aqueous solution was extracted with DCM : MeOH = 10:1 (1.5 L). The organic layer was dried and concentrated to afford 6.3 g of 1-cyclopropyl-1H-1,2,3-triazole-4-carboxylic acid as white solid. The aqueous layer was concentrated to afford another 11.4 g crude product, which was used for next step without further purification. ESI-LCMS (m/z): 154.1 $[\text{M}+\text{H}]^+$.

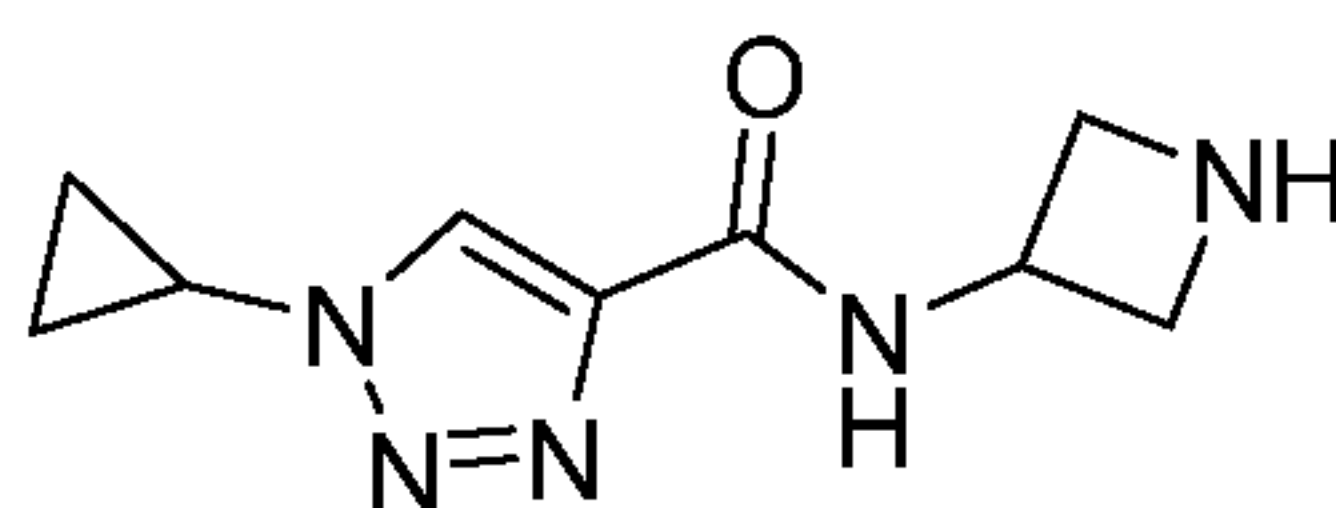
Step 4: Synthesis of tert-butyl 3-(1-cyclopropyl-1H-1,2,3-triazole-4-carboxamido)azetidine-1-carboxylate



[0354] A solution of 1-cyclopropyl-1H-1,2,3-triazole-4-carboxylic acid (2 g, 13.0 mmol) in thionyl chloride (10 mL) was stirred at 65 °C for 2h. The reaction mixture was concentrated under reduced pressure. Then the reaction residue was diluted with DMF (5

mL) and added dropwise to the solution of tert-butyl 3-aminoazetidine-1-carboxylate (2.23 g, 13.0 mmol) and DIPEA (4.19 g, 32.5 mmol) in DCM (15 mL) under 0 °C. The resulting mixture was stirred at room temperature overnight. The solvent was removed and the residue was diluted with ethyl acetate (200 mL), washed with water (10 mL x3) and brine (50 mL), dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by Flash chromatography (DCM: NH₃ in MeOH(7N)=100:0~50:1) to give tert-butyl 3-(1-cyclopropyl-1H-1,2,3-triazole-4-carboxamido)azetidine-1-carboxylate (3 g, 75.1 %) as a yellow solid. ESI-LCMS (m/z): 252.2 [M-55]⁺.

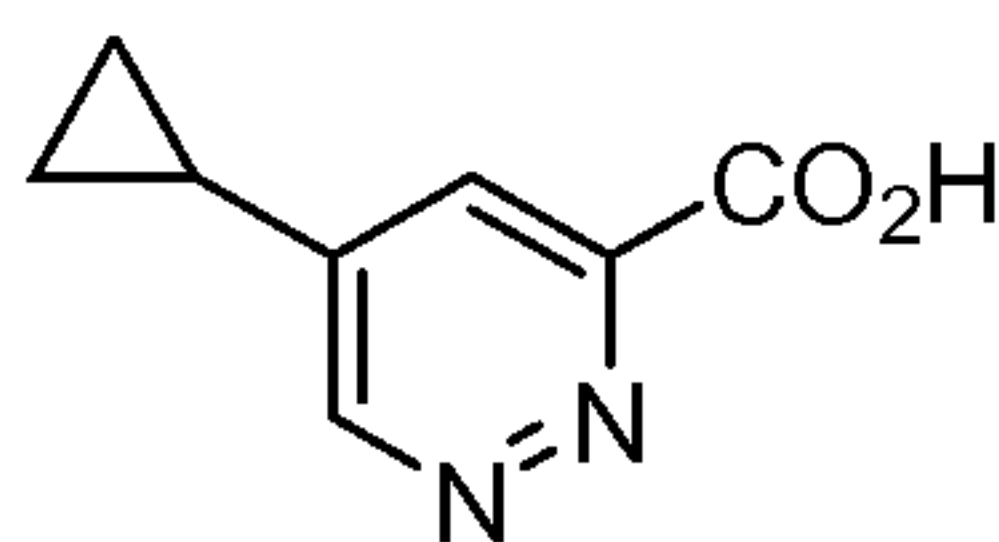
Step 5: Synthesis of N-(Azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide



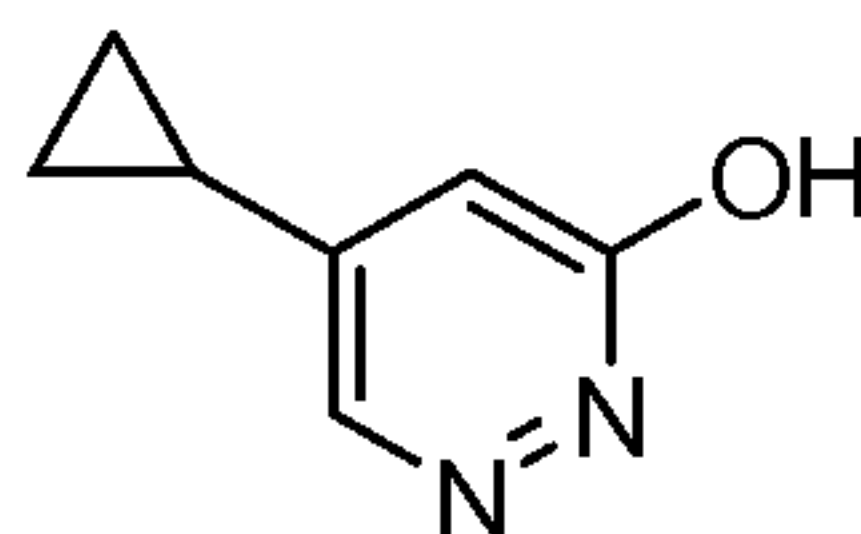
[0355] A solution of tert-butyl 3-(1-cyclopropyl-1H-1,2,3-triazole-4-carboxamido)azetidine-1-carboxylate (3.0 g, 9.8 mmol) in HCl/MeOH (20 mL) was stirred at 50 °C for 2h. After completion, the solvent was removed in vacuo. The residue was dissolved in NH₃/MeOH (7 mol/L, 20 mL) and stirred for 30 min. The solvent was removed and the residue was purified by Flash chromatography (DCM: NH₃ in MeOH(7N)=100:0 ~30:1~15:1) to give N-(azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide (1.6 g, 80 %) as a white solid. ESI-LCMS (m/z): 208.1 [M+H]⁺. ¹H-NMR (400 MHz, CD₃OD) δ ppm: 8.38 (s, 1H), 4.92-4.86 (m, 1H), 3.98-3.97 (m, 1H), 3.82-3.72 (m, 4H), 1.26-1.20 (m, 4H).

EXAMPLE 25

Synthesis of 5-cyclopropylpyridazine-3-carboxylic acid



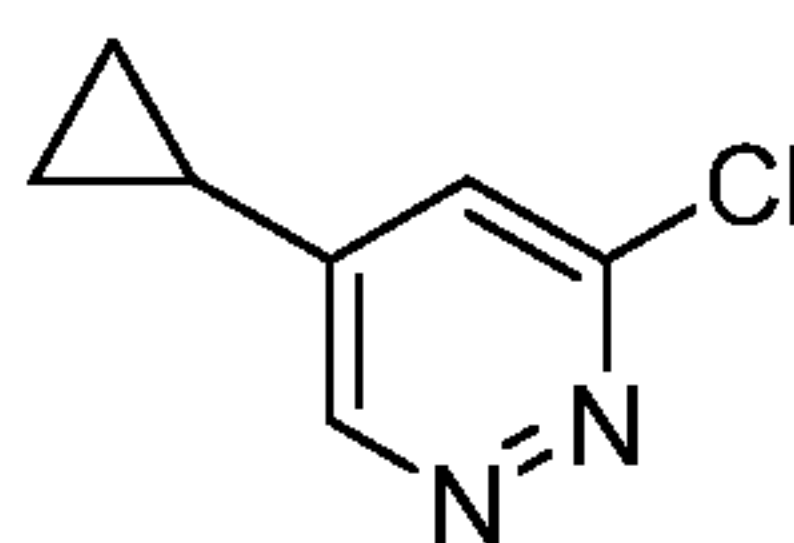
Step 1: Synthesis of 5-cyclopropylpyridazin-3-ol



[0356] To a solution of 5-chloropyridazin-3-ol (1.0 g, 7.7 mmol) in toluene/H₂O (100: 5, 50 mL) was added sequentially cyclopropylboronic acid (987 mg, 11.5 mmol), K₃PO₄

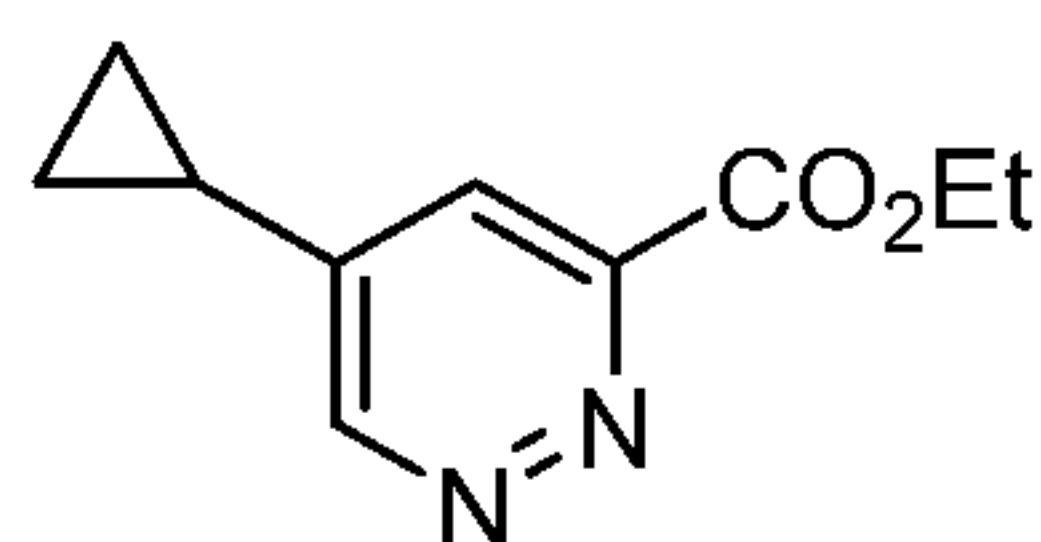
(4.51 g, 23.0 mmol), diacetoxypalladium (86.2 mg, 384 μ mol) and tricyclohexylphosphine (107 mg, 384 μ mol). The reaction mixture was stirred at 100 °C under N₂ atmosphere for 20 h. then concentrated in vacuum to remove the solvent Water (20 mL) was added and the solution was acidified with hydrochloric acid (4 M) to pH = 3. The solution was extracted with EtOAc (200 mL x 3) and the combined organic layer were washed with saturated NaCl solution, dried over Na₂SO₄, concentrated to give a brown residue then purified by silica-gel chromatography (PE: EA = 1:1) to afford the desired product (350 mg, 34 % yield) as white solid. ESI-LCMS (m/z): 137.1 [M+1]⁺.

Step 2: Synthesis of 3-chloro-5-cyclopropylpyridazine



[0357] A solution of 5-cyclopropylpyridazin-3-ol (350 mg, 2.6 mmol) in phosphorous oxychloride (10 mL) was stirred at 80 °C for 2 h. The remaining POCl₃ was removed under vacuum then the residue was cooled and added to 20 g of ice. The reaction mixture was neutralized with saturated NaHCO₃ solution and extracted with EtOAc (40 mL x 3), the combined organic extract is washed with brine (100 mLx2), dried over Na₂SO₄ and the solvent is removed under vacuum. the resulting residue was purified by silica-gel chromatography (PE: EA = 2:1) to afford the product 3-chloro-5-cyclopropylpyridazine as a colorless oil (200 mg, 50% yield). ESI-LCMS (m/z): 155.2 [M+1]⁺.

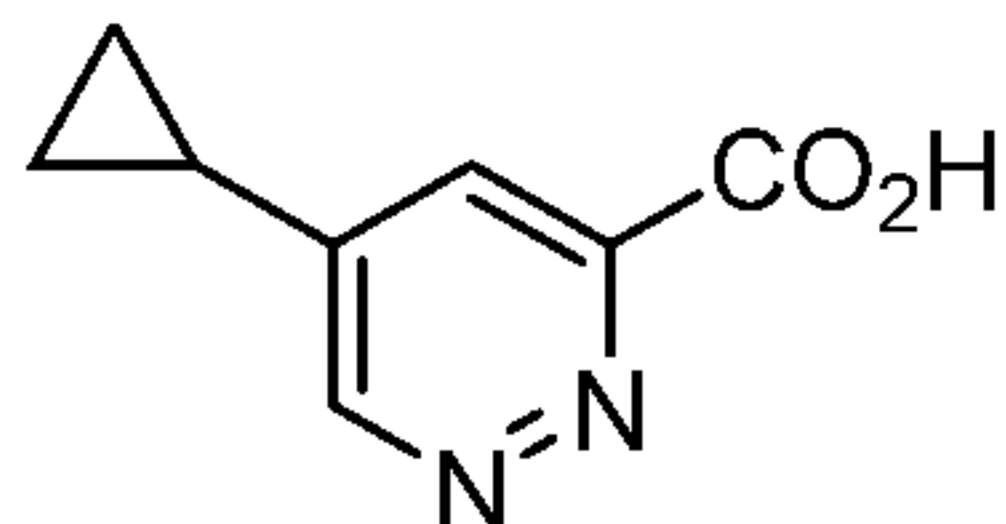
Step 3: Synthesis of ethyl 5-cyclopropylpyridazine-3-carboxylate



[0358] Potassium acetate (284 mg, 2.9 mmol) was added to a solution of 3-chloro-5-cyclopropylpyridazine (150 mg, 1.0 mmol) in ethanol (10 mL). The mixture was degassed, then Pd(dppf)Cl₂ (35.4 mg, 0.05 mmol) was added. The resulting mixture was heated under an atmosphere of CO at 70°C for 20 hr. The reaction mixture was filtrated and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA = 1:1) to obtain the desired product ethyl 5-cyclopropylpyridazine-3-carboxylate (100 mg, 54% yield, colorless oil). ESI-LCMS (m/z): 193.1 [M+H]⁺ ; ¹HNMR (400 MHz, CD₃OD) δ ppm: 9.06 (d, J = 2.4 Hz, 1H),

7.81 (d, $J = 2.4$ Hz, 1H), 7.39 (q, $J = 6.8$ Hz, 2H), 2.11-1.92 (m, 1H), 1.34 (t, $J = 6.8$ Hz, 3H), 0.96-0.93 (m, 2H).

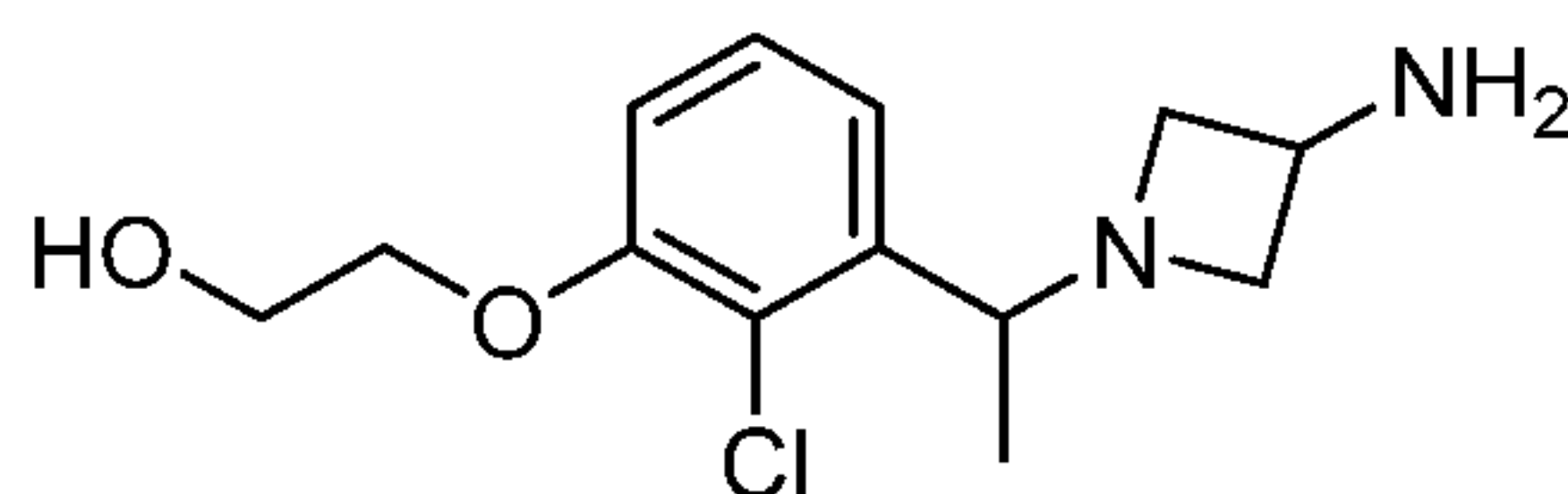
Step 4: Synthesis of 5-cyclopropylpyridazine-3-carboxylic acid



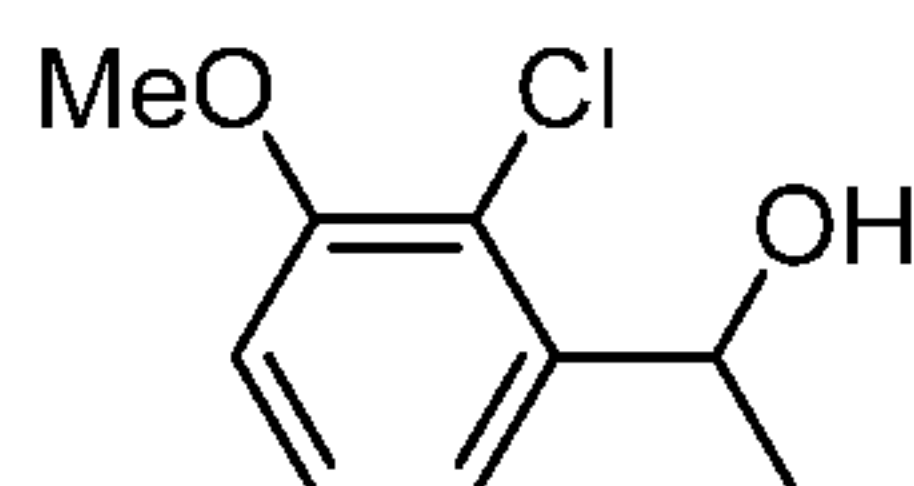
[0359] To a solution of methyl 5-cyclopropylpyridazine-3-carboxylate (185 mg, 1.03 mmol) in THF/H₂O (8 mL/2 mL) was added lithium hydroxide hydrate (64.6 mg, 1.54 mmol). The reaction mixture was stirred at room temperature for 3h. Progress of the reaction was monitored by TLC and LCMS. After completion, the mixture was adjusted to pH= 5 with 1N HCl, then concentrated directly to 5-cyclopropylpyridazine-3-carboxylic acid (170 mg, 94.6 %) as yellow solid and used in next step directly. ESI-LCMS (m/z): 165 $[M+1]^+$.

EXAMPLE 26

Synthesis of 2-(3-(1-(3-Aminoazetidin-1-yl)ethyl)-2-chlorophenoxy)ethan-1-ol

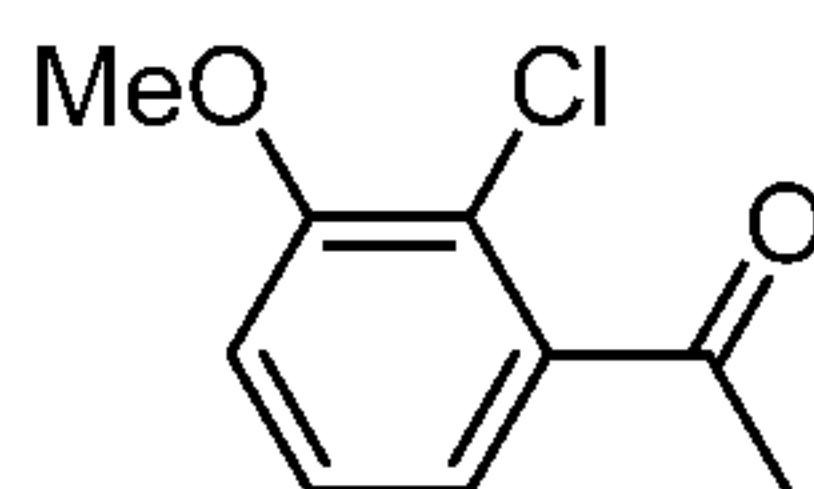


Step 1: Synthesis of 1-(2-chloro-3-methoxyphenyl)ethanol



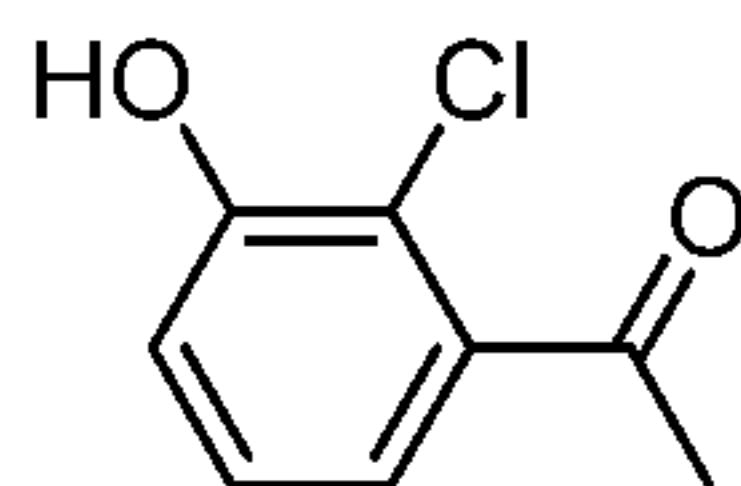
[0360] A mixture of 2-chloro-3-methoxybenzaldehyde (2.38 g, 14 mmol) in THF (50 mL) was stirred at 0 °C, and a solution of methylmagnesium bromide (5.6 mL, 16.7 mmol, 3M) in ether was added. The resulting mixture was stirred overnight. The reaction mixture was diluted with 1 N HCl (50 mL) and extracted with ethyl acetate (50 mL x3), the combined organic phase was washed with brine, dried over sodium sulfate and concentrated to afford 1-(2-chloro-3-methoxyphenyl)ethanol (2.60 g, 99.6 %) as a yellow oil. ¹HNMR (400 MHz, CD₃OD) δ ppm: 7.49 (d, $J = 8.4$ Hz, 1 H), 6.90-6.85 (m, 2 H), 5.25 (q, $J = 6.4, 12.8$ Hz, 1 H), 3.81 (s, 3 H), 1.48 (d, $J = 6.4$ Hz, 3 H).

Step 2: Synthesis of 1-(2-chloro-3-methoxyphenyl)ethanone



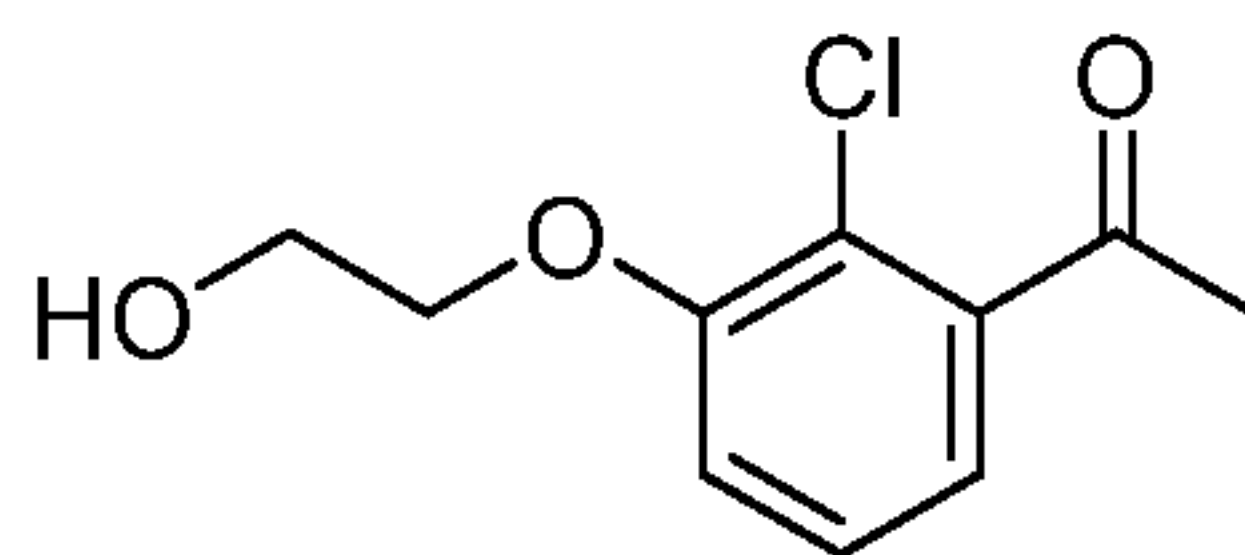
[0361] A mixture of 1-(2-chloro-3-methoxyphenyl)ethanol (2.0 g, 10.7 mmol) and manganese(IV) oxide (4.65 g, 53.5 mmol) in DCM (50 mL) was heated to 40 °C and stirred overnight. The reaction mixture was filtered through Celite and the filtrate was concentrated to afford 1-(2-chloro-3-methoxyphenyl)ethanone (1.83 g, 89.8 %) as a yellow oil. ESI-LCMS (m/z): 185.0 [M+1]⁺.

Step 3: Synthesis of 1-(2-chloro-3-hydroxyphenyl)ethanone



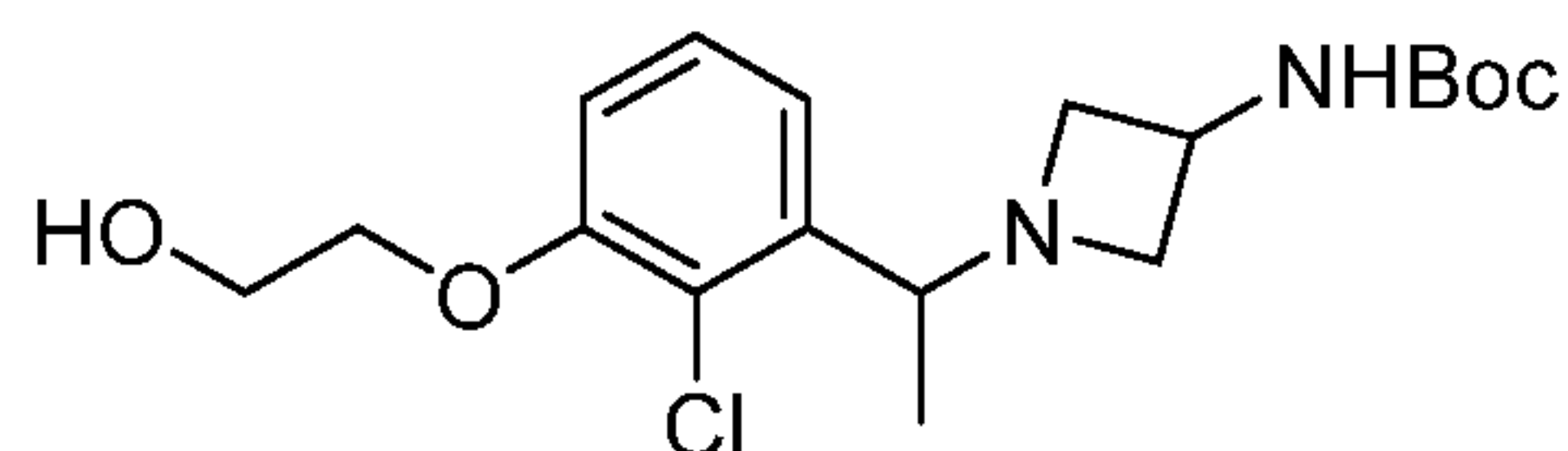
[0362] A mixture of 1-(2-chloro-3-methoxyphenyl)ethanone (540 mmol, 2.92 mmol) and aluminum trichloride (972 mg, 7.29 mmol) in monochlorobenzene (10 mL) was stirred at 120 °C for 2 hrs. After cooling to rt, the reaction mixture was added dropwise into 1N HCl in a water bath and the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography (PE:EA = 5:1) to afford 1-(2-chloro-3-hydroxyphenyl)ethanone (400 mg, 80.3 %) as a yellow solid ESI-LCMS (m/z): 171.0[M+H]⁺.

Step 4: Synthesis of 1-(2-chloro-3-(2-hydroxyethoxy)phenyl)ethanone



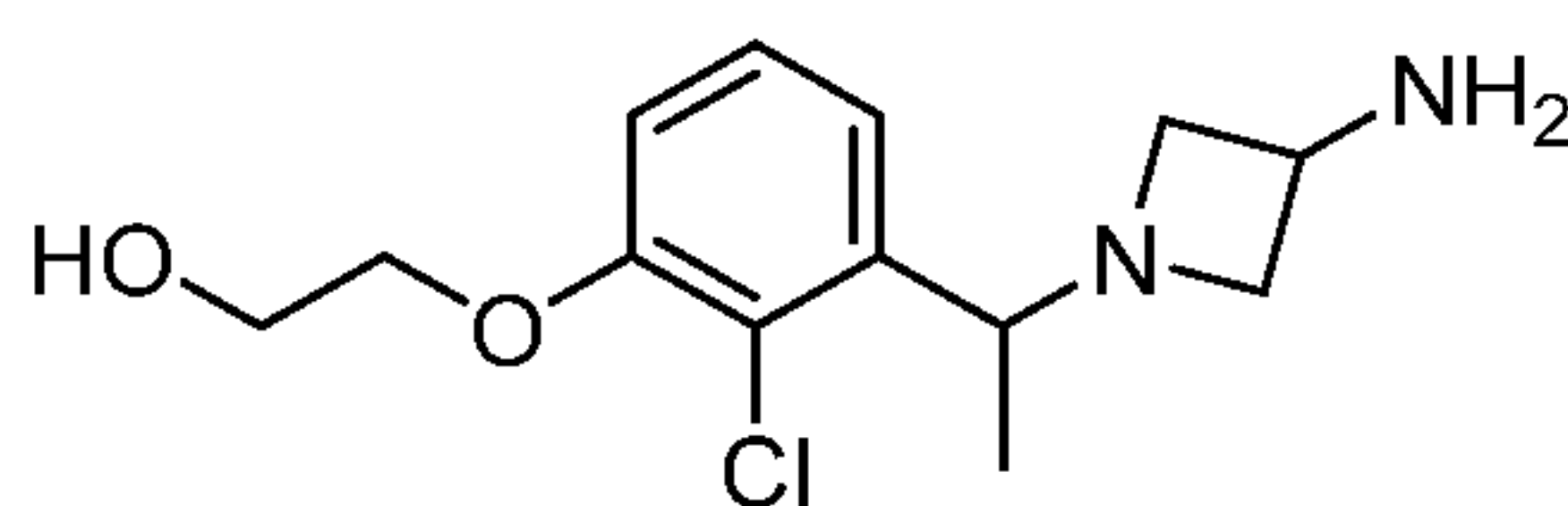
[0363] A mixture of 1-(2-chloro-3-hydroxyphenyl)ethanone (330 mg, 1.93 mmol), 2-bromoethanol (482 mg, 3.86 mmol) and K₂CO₃ (800 mg, 5.79 mmol) in DMF (10 mL) was heated to 80 °C overnight. Water was added and the mixture was extracted with ethyl acetate (30 mL x 3), the combined organic phase was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography (DCM: MeOH = 50:1) to afford 1-(2-chloro-3-(2-hydroxyethoxy) phenyl)ethanone (400 mg, 79.2 %) as a yellow oil. ESI-LCMS (m/z): 251.1 [M+H]⁺.

Step 5: Synthesis of tert-butyl 1-(1-(2-chloro-3-(2-hydroxyethoxy)phenyl)ethyl)azetidin-3-ylcarbamate



[0364] A mixture of 1-(2-chloro-3-(2-hydroxyethoxy)phenyl)ethanone (214 mg, 1 mmol), tert-butyl azetidin-3-ylcarbamate (206 mg, 1.20 mmol), acetic acid (120 mg, 2.00 mmol) and NaBH_3CN (125 mg, 2.00 mmol) in MeOH (10 ml) was stirred at 70 °C overnight. The reaction mixture was concentrated and adjusted pH = 8-9 with a saturated solution of Na_2CO_3 . The resulting mixture was extracted with DCM (30 mL x3) and the combined organic phase was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by prep-TLC (DCM: MeOH = 20:1) to afford tert-butyl (1-(1-(2-chloro-3-(2-hydroxyethoxy)phenyl)ethyl)azetidin-3-yl) carbamate (220 mg, 52.7 %) as a yellow oil. ESI-LCMS (m/z): 371.2 $[\text{M}+1]^+$.

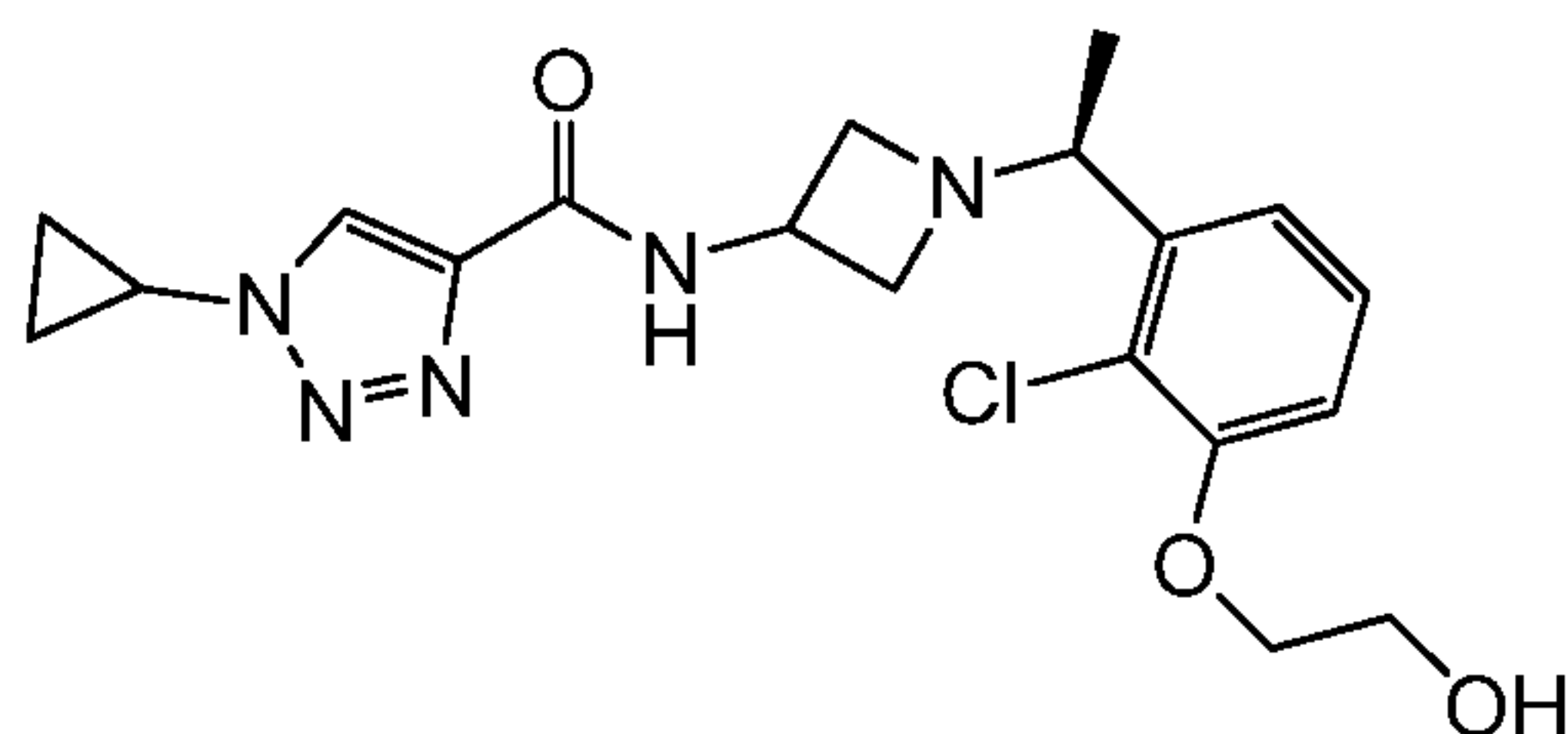
Step 6: Synthesis of 2-(3-(1-(3-Aminoazetidin-1-yl)ethyl)-2-chlorophenoxy)ethanol



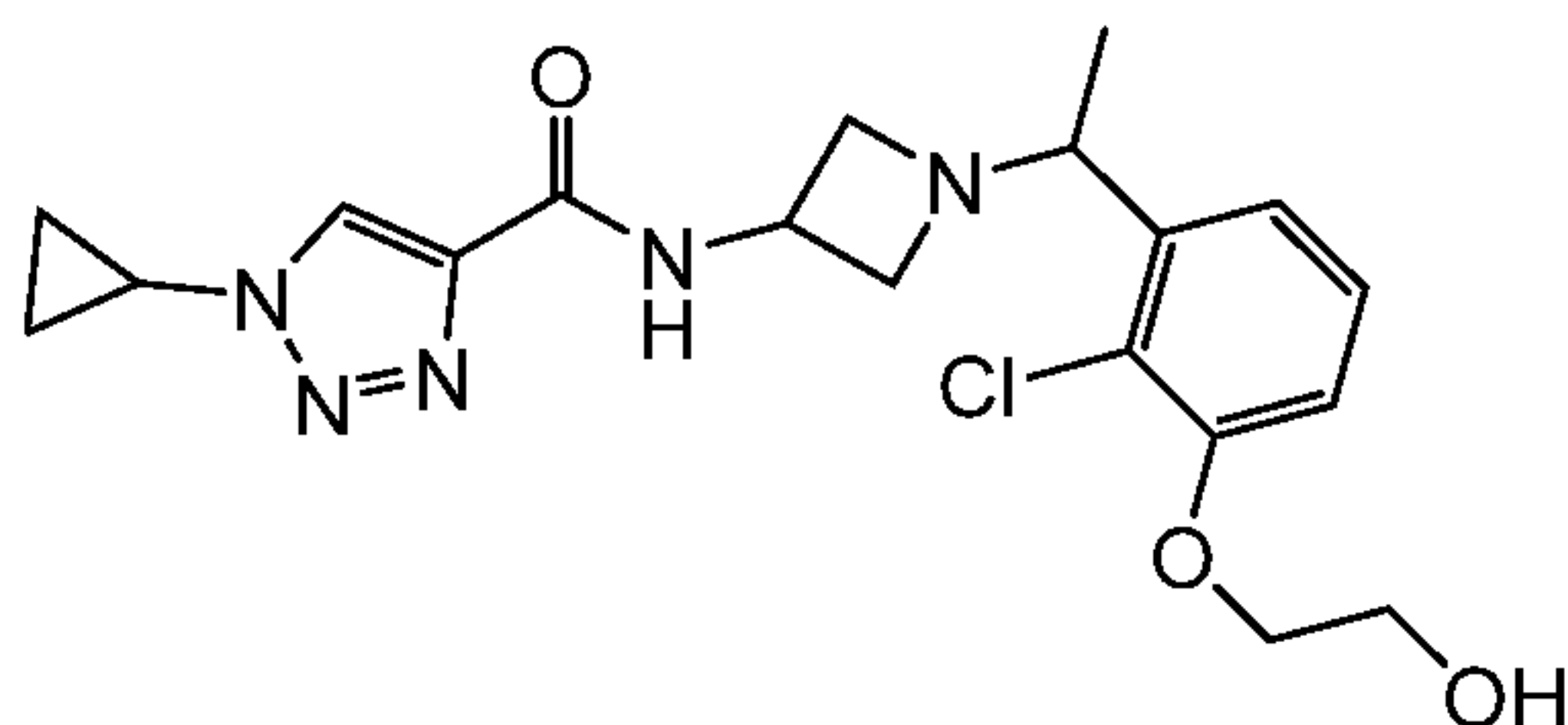
[0365] A mixture of tert-butyl (1-(1-(2-chloro-3-(2-hydroxyethoxy)phenyl)ethyl) and azetidin-3-yl)carbamate (200 mg, 539 μmol) in a solution of HCl/MeOH (10 mL, 3N) was stirred at rt for 3 hrs. The reaction mixture was concentrated under reduced pressure to afford 2-(3-(1-(3-aminoazetidin-1-yl)ethyl)-2-chlorophenoxy)ethanol (120 mg, 68.9 %) as a yellow oil. ESI-LCMS (m/z): 271.2 $[\text{M}+1]^+$.

EXAMPLE 27

Synthesis of (S)-N-(1-(1-(2-chloro-3-(2-hydroxyethoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide (Cpd. No. 831)

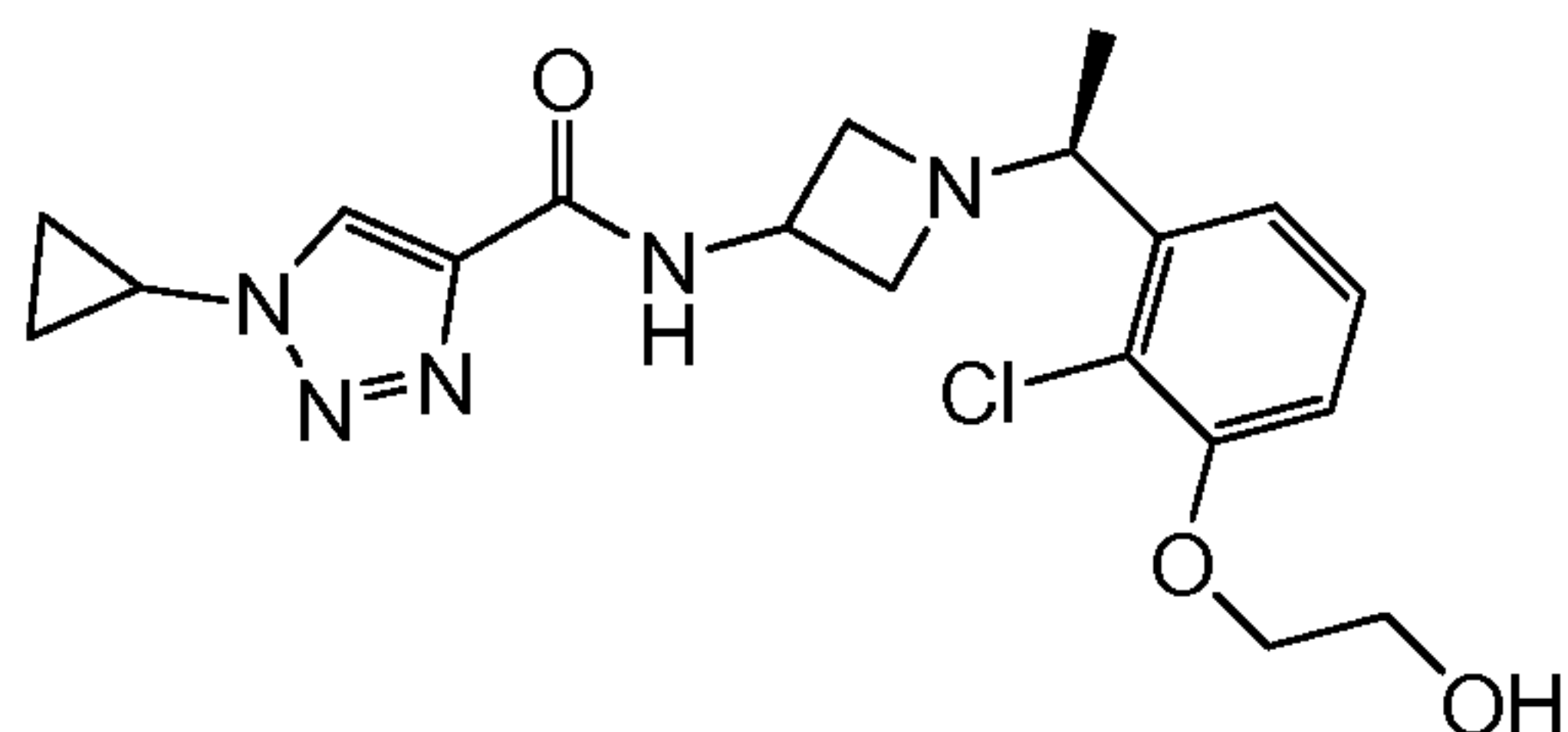


Step 1: Synthesis of N-(1-(1-(2-Chloro-3-(2-hydroxyethoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide



[0366] A mixture of 1-cyclopropyl-1H-1,2,3-triazole-4-carboxylic acid (22.9 mg, 150 μ mol), 2 (3-(1-(3-aminoazetidin-1-yl)ethyl)-2-chlorophenoxy)ethanol (40.6 mg, 0.15 mmol), HATU (85.4 mg, 225 μ mol) and DIPEA (38.6 mg, 300 μ mol) in DMF (2 mL) was stirred at rt for 2 h. water was added and the mixture was extracted with ethyl acetate (10 mL x3), the combined organic phase was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by Pre-TLC (DCM: MeOH = 20:1) to afford N-(1-(1-(2-chloro-3-(2-hydroxyethoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide (15 mg, 24.6 %) as a white solid. ESI-LCMS (m/z): 406.1 [M+23]⁺. ¹HNMR (400 MHz, CD₃OD) δ ppm: 8.38 (s, 1 H), 7.43 (d, J = 8.4 Hz, 1 H), 7.00-6.93 (m, 2 H), 4.66-4.59 (m, 1 H), 4.06-3.95 (m, 4 H), 3.89-3.86 (m, 2 H), 3.83-3.79 (m, 1 H), 3.53-3.50 (m, 1 H), 3.22 (t, J = 7.2 Hz, 1 H), 3.04 (t, J = 7.2 Hz, 1 H), 1.30-1.19 (m, 7 H).

Step 2: Synthesis of (S)-N-(1-(1-(2-chloro-3-(2-hydroxyethoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide

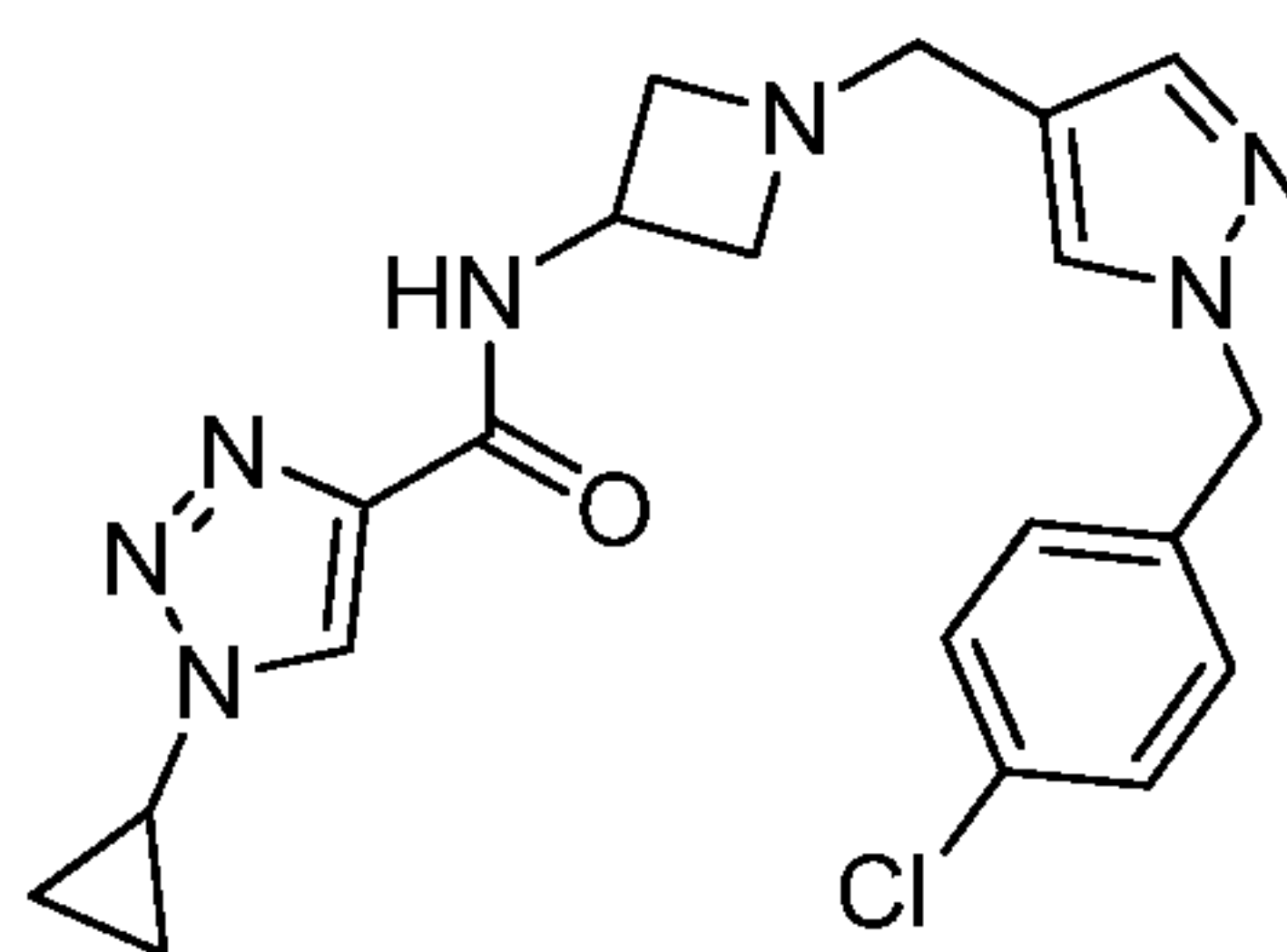


[0367] N-(1-(1-(2-chloro-3-(2-hydroxyethoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide (350 mg, 862 μ mol) was separated by chiral HPLC to obtain two single enantiomers, (isomer1:160 mg, white solid, Ret time 5.02 min; isomer 2:170 mg, Ret time 6.51 min), absolute stereochemistry is undefined, the isomer (Ret time:5.02 min) was assumed to be S configuration, (S)-N-(1-(1-(2-chloro-3-(2-hydroxyethoxy)phenyl)ethyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide (160 mg, 45.8 %) as a white solid. ESI-LCMS (m/z): 406.2 [M+1]⁺. ¹HNMR (400 MHz, CD₃OD) δ ppm: 8.38 (s, 1 H), 7.44 (d, J = 8.4 Hz, 1 H), 6.99-6.94 (m, 2 H), 4.63 (t, J = 7.2 Hz, 1 H), 4.06-3.98 (m, 4 H), 3.89-3.86 (m, 2 H), 3.82 (t, J = 7.2 Hz, 1 H), 3.52 (t, J = 7.2 Hz, 1 H), 3.22 (t, J = 7.2 Hz, 1 H), 3.05 (t, J = 7.2 Hz, 1 H),

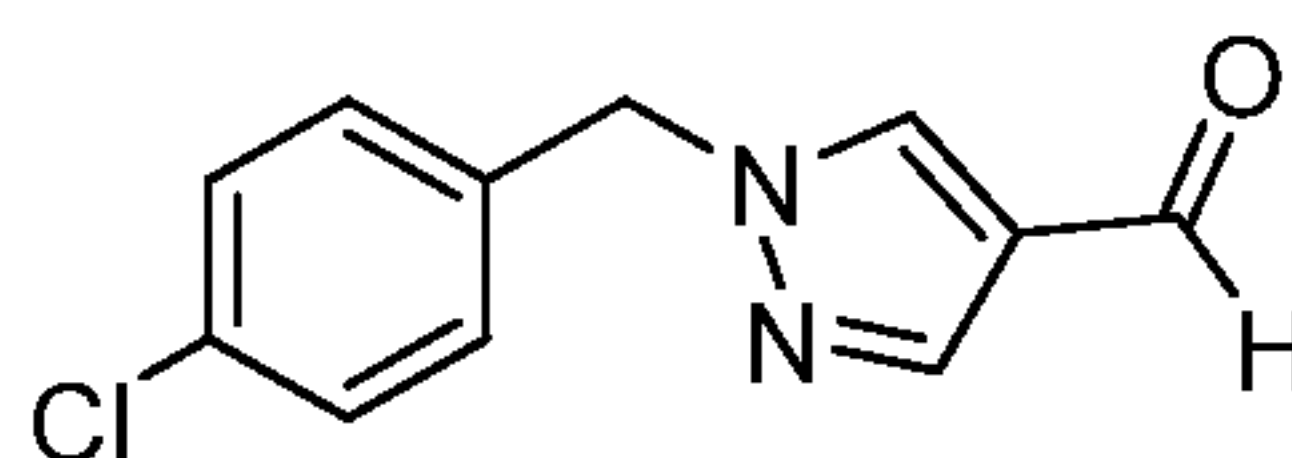
1.27-1.21 (m, 7 H). SFC conditions: Instrument: SFC-80 (Thar, Waters) t; Column: REGISCELL 20*250mm, 5um (Dacel); Column temperature: 35 °C; Mobile phase: CO₂/MEOH(0.2% methanol amina) = 60/40; Flow rate: 80 g/min; Back pressure: 100 bar; Detection wavelength: 214 nm; Cycle time: 8.8 min; Sample solution: 350 mg dissolved in 15 ml Methanol; Injection volume: 3 mL.

EXAMPLE 28

Synthesis of N-(1-((1-(4-Chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide (Cpd. No. 985)

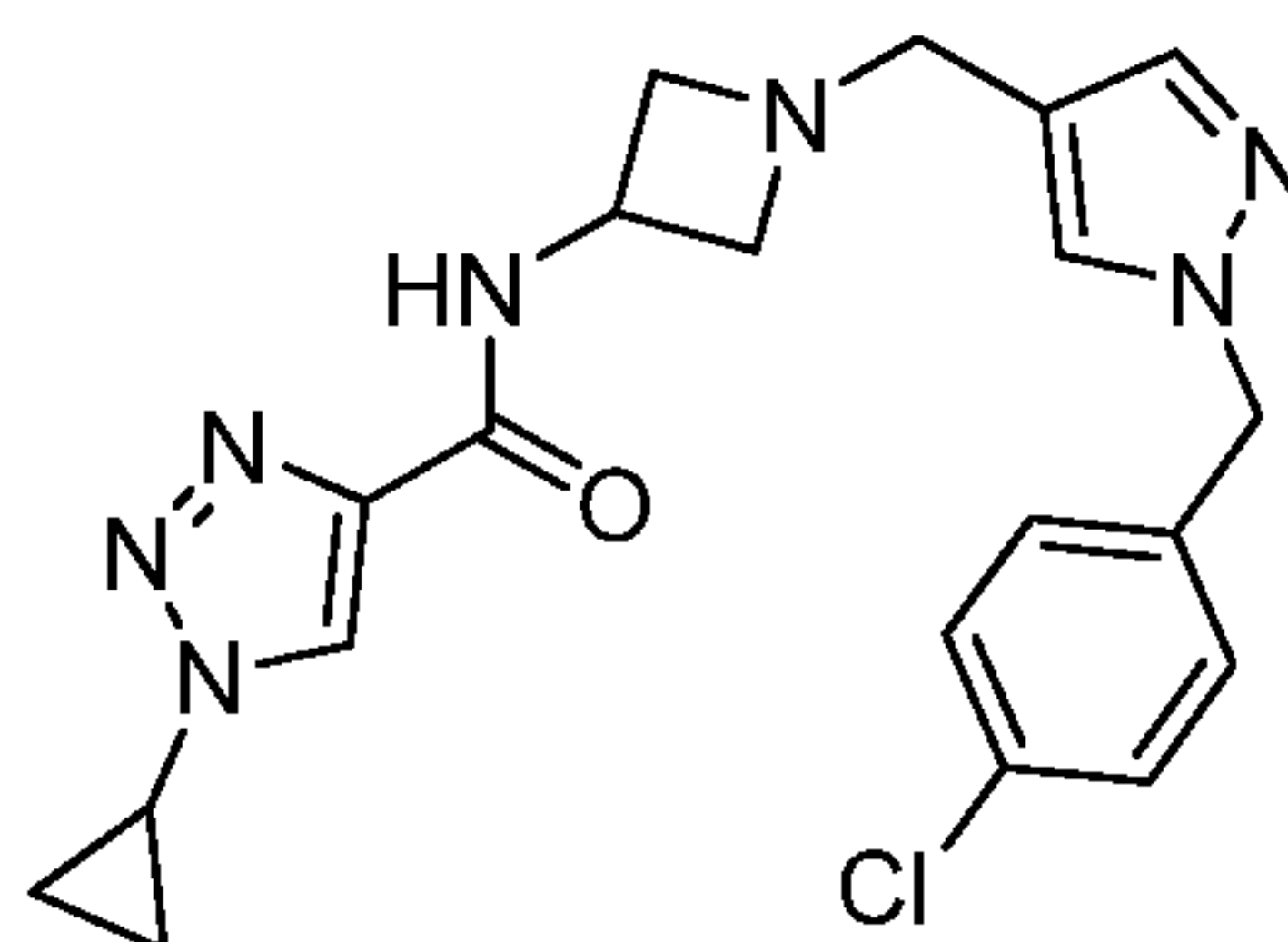


Step 1: Synthesis of 1-(4-Chlorobenzyl)-1H-pyrazole-4-carbaldehyde



[0368] To a solution of 1H-pyrazole-4-carbaldehyde (70 mg, 728 μmol) in MeCN (5 mL) was added 1-(bromomethyl)-4-chlorobenzene (149 mg, 728 μmol) and cesium carbonate (472 mg, 1.45 mmol). The mixture was stirred at r.t. for 2h. The mixture was concentrated, diluted with EA and water. The organic phase was washed with brine (10 mL x 2), dried over Na₂SO₄ and concentrated to give 1-(4-chlorobenzyl)-1H-pyrazole-4-carbaldehyde (162 mg, 101 %) as a white solid, which was used in the next step without further purification. ESI-LCMS (m/z): 221[M+H]⁺.

Step 2: Synthesis of N-(1-((1-(4-Chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide

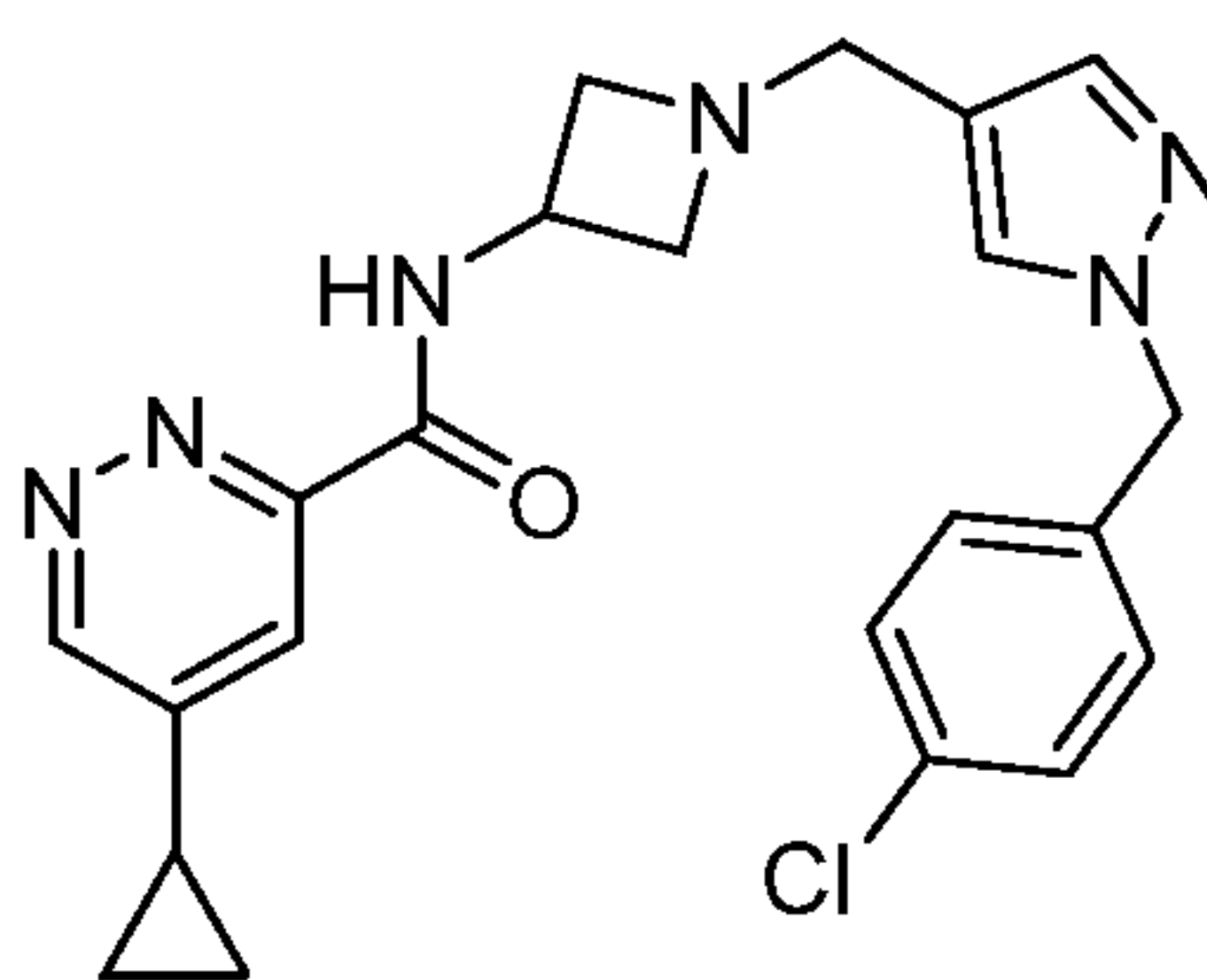


[0369] A mixture of N-(azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide (62 mg, 299 μmol), 1-(4-chlorobenzyl)-1H-pyrazole-4-carbaldehyde (65.9 mg,

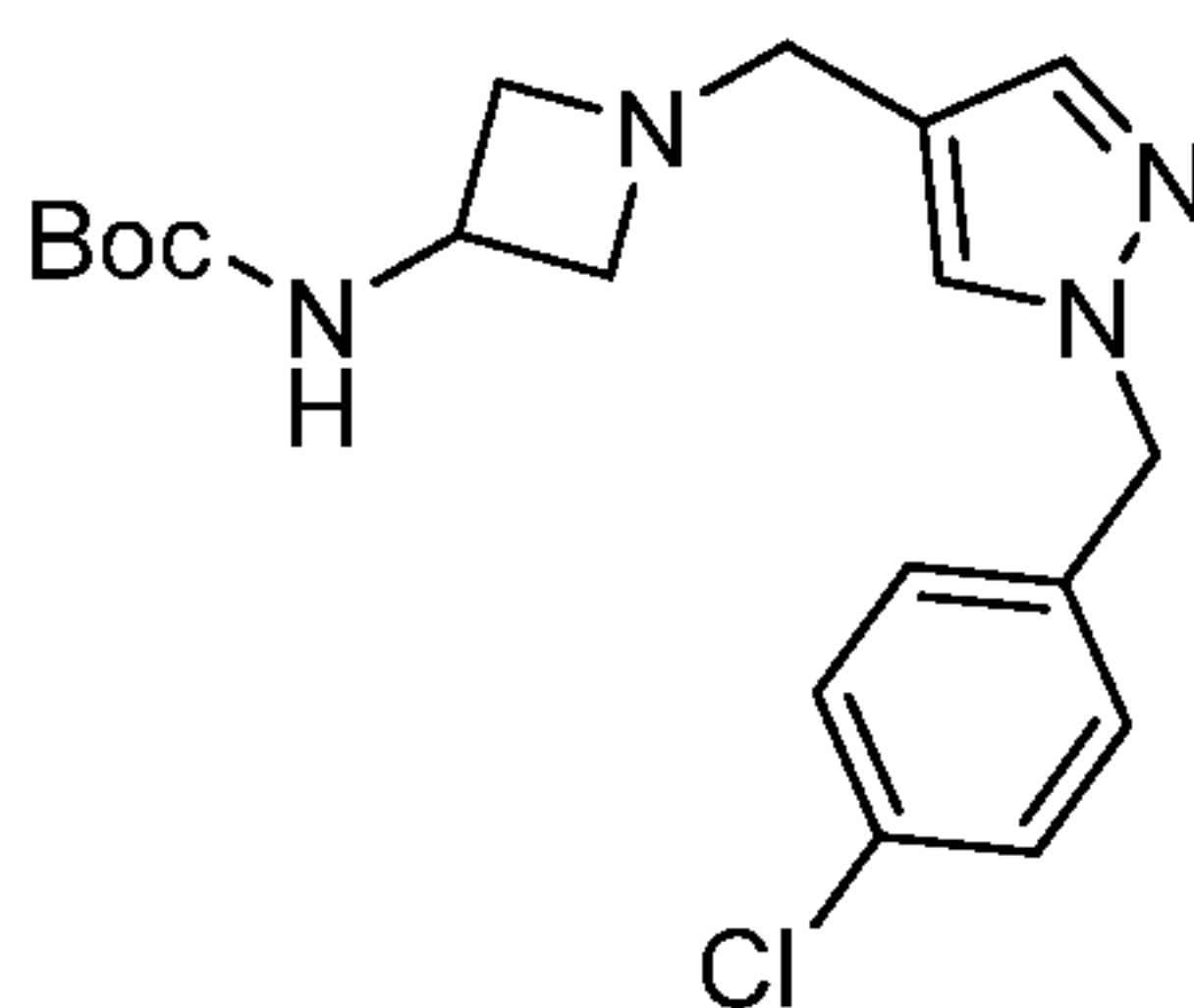
299 μmol), and sodium cyanoborohydride (56.3 mg, 897 μmol) in MeOH (10 mL) was stirred at 60 °C for 16h. The mixture was cooled and concentrated. The residue was diluted with EA, washed with water (10 mL) and brine (10 mL x 2), dried over Na_2SO_4 and concentrated. The residue was purified by prep-HPLC to give N-(1-(((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide (70 mg, 56.9 %) as a white solid. ESI-LCMS (m/z): 412 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CD_3OD) δ ppm: 8.38 (s, 1 H), 7.67 (s, 1 H), 7.50 (s, 1 H), 7.35 (d, $J=8.0$ Hz, 2H), 7.21(d, $J=8.0$ Hz, 2H), 5.31(s, 2H), 4.65-4.61 (m, 1H), 4.00-3.96 (m, 1H), 3.71-3.67 (m, 2H), 3.61 (s, 2H), 3.22(t, $J=8.0$ Hz, 2H), 1.30-1.24 (m, 2H), 1.21-1.19 (m, 2H).

EXAMPLE 29

Synthesis of N-(1-(((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide (Cpd No. 929)



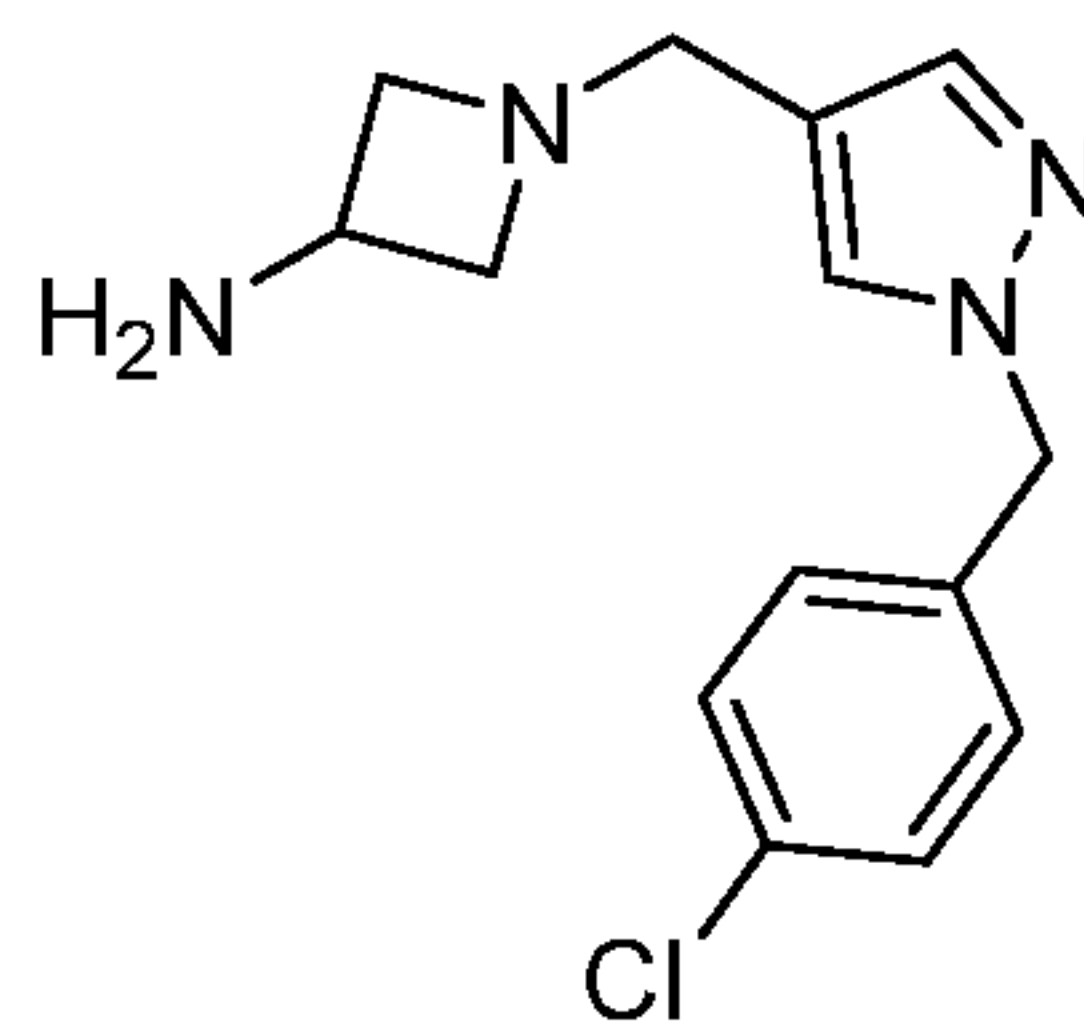
Step 1: Synthesis of tert-butyl (1-(((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)carbamate



[0370] A mixture of 1-(4-chlorobenzyl)-1H-pyrazole-4-carbaldehyde (200 mg, 0.9063 mmol), tert-Butyl (azetidin-3-yl)carbamate hydrochloride (377 mg, 1.81 mmol) and acetic acid (54.4 mg, 0.9063 mmol) were dissolved in MeOH (40 ml). After stirred for 2h at r.t., sodium cyanoborohydride (142 mg, 2.26 mmol) was added to the solution. The mixture was stirring over night at r.t.. Then, the solution was concentrated under reduced pressure and the residue purified by flash column chromatography (eluant: DCM : MeOH = 10:1 (600 ml)). To furnish tert-butyl (1-(((1-(4-chlorobenzyl)-1H-pyrazol-4-

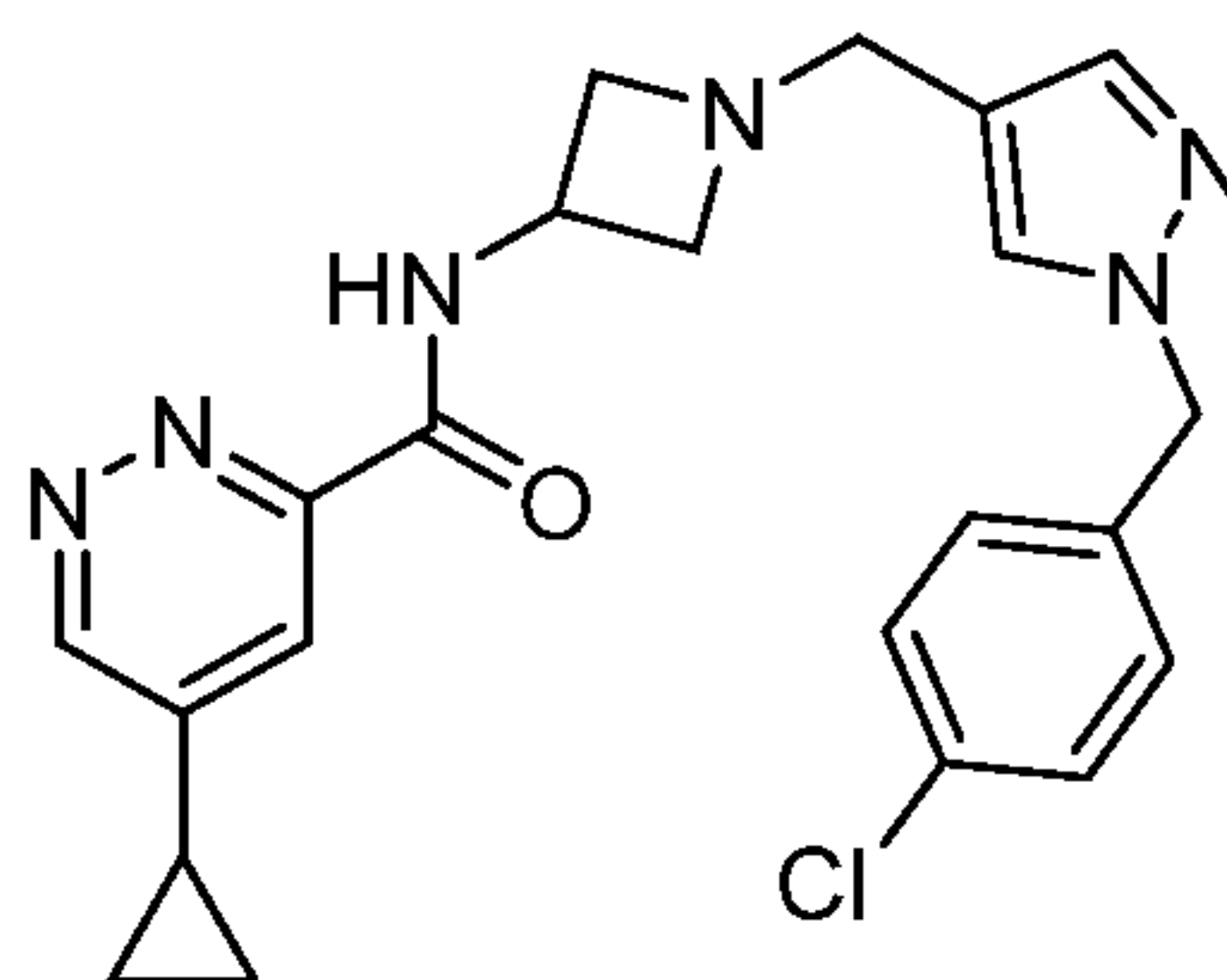
yl)methyl)azetidin-3-yl)carbamate (273 mg, 54.2 %) as colorless oil. ESI-LCMS (m/z): 377[M+H]⁺.

Step 2: Synthesis of 1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-amine



[0371] tert-Butyl 1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)carbamate (273 mg, 0.4908 mmol) was dissolved in HCl in MeOH (3M) (20 ml). The solution was stirring over night at 50 °C. After cooled to r.t., the solution was concentrated to afford 1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-amine (200 mg, 71.7 %) as yellow solid, which was used for next step without purification. ESI-LCMS (m/z): 277[M+H]⁺.

Step 3: Synthesis of N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide

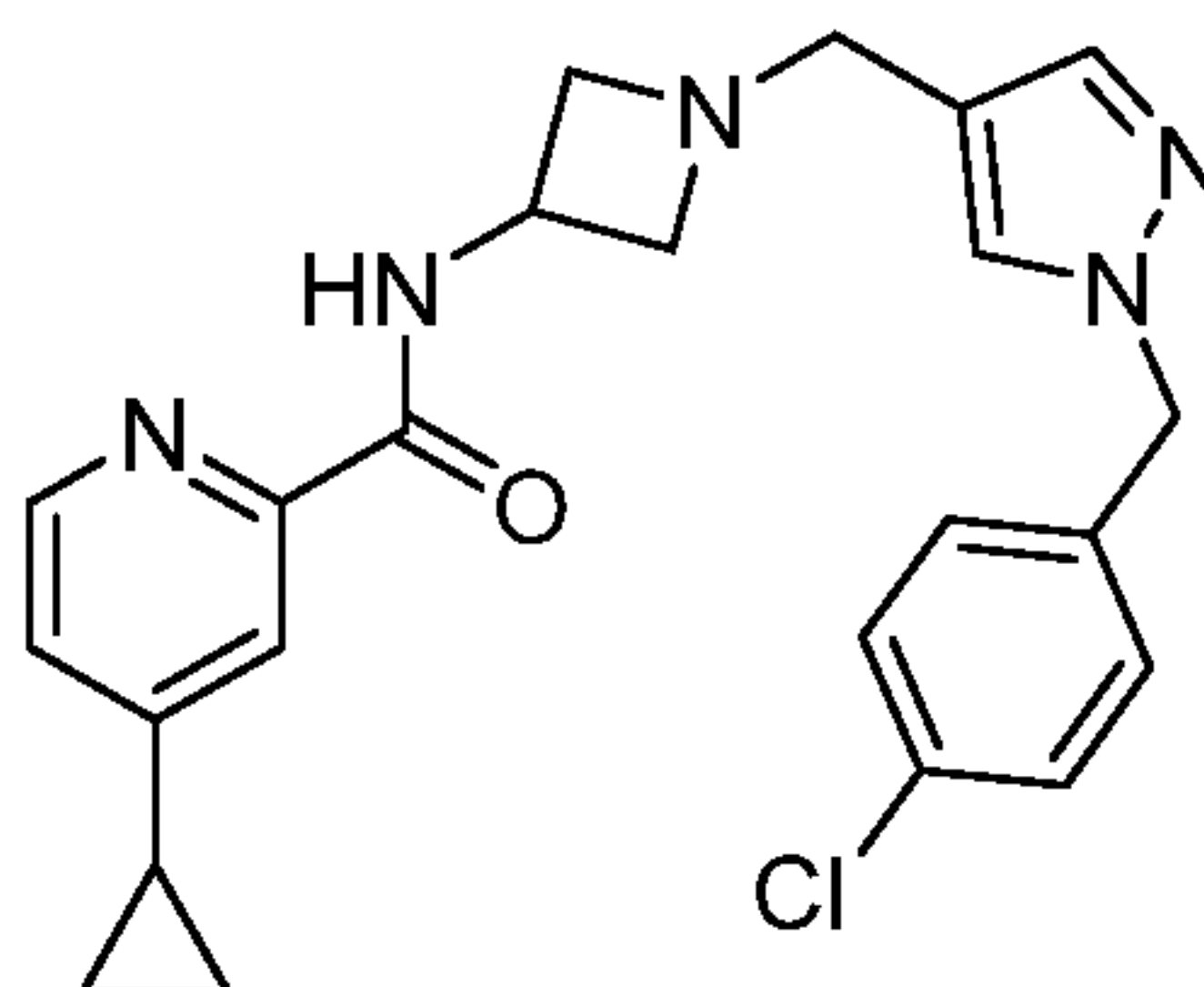


[0372] 5-cyclopropylpyridazine-3-carboxylic acid (60 mg, 0.3654 mmol) and HATU (250 mg, 0.6577 mmol) were dissolved in DMF (6 ml). After stirred for 1h at r.t., 1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-amine (219 mg, 0.3836 mmol) and triethylamine (110 mg, 1.09 mmol) were added to the solution. Then, the mixture was stirring for 4h at r.t.. Then, ethyl acetate (100 ml) was added and the ethyl acetate layer was washed by brine (50 mL X 1), dried by Na₂SO₄, and concentrated. The residue was purified by Prep-HPLC to afford N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide (72 mg, 46.7 %) as white solid. ESI-LCMS (m/z): 423[M+H]⁺; ¹HNMR (400 MHz, CD₃OD) δ ppm: 9.15 (s, 1H), 7.86 (s, 1H), 7.69 (s, 1H), 7.51 (s, 1H), 7.36-7.32 (m, 2H), 7.20 (d, J=8.4 Hz, 2H),

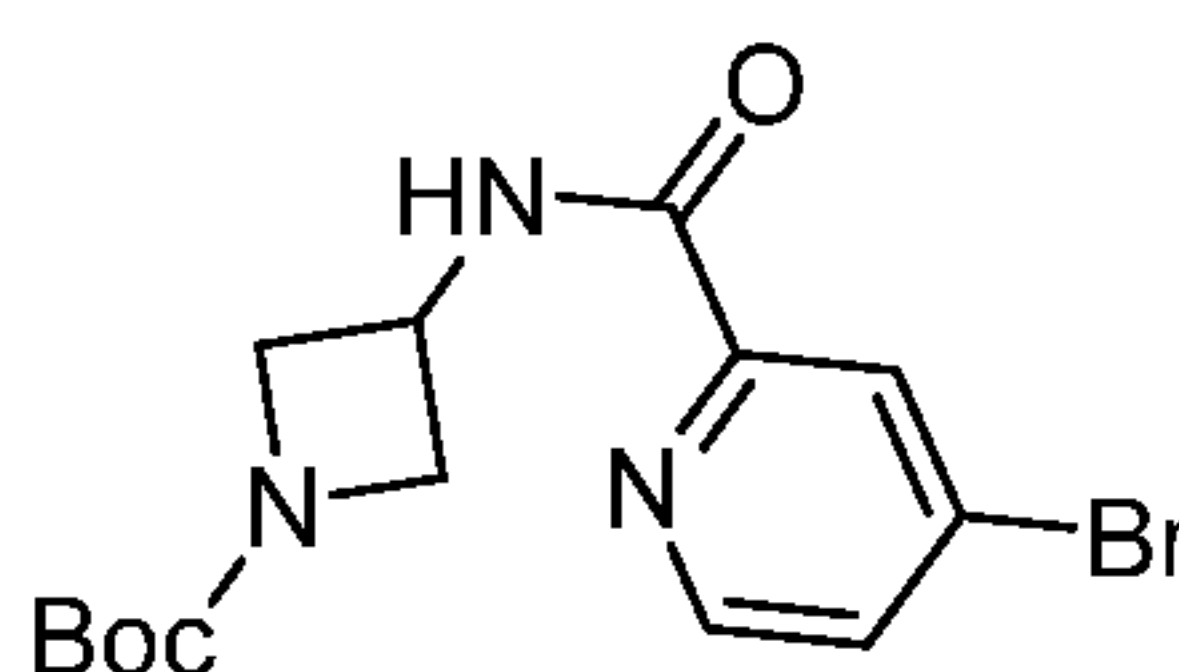
5.32 (s, 2H), 4.72-4.68 (m, 1H), 3.74-3.70 (m, 2H), 3.63 (s, 2H), 3.30-3.26 (m, 2H), 2.12-2.08 (m, 1H), 1.33-1.28 (m, 2H), 1.04-1.00 (m, 2H).

EXAMPLE 30

Synthesis of N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-4-cyclopropylpicolinamide (Cpd. No. 930)

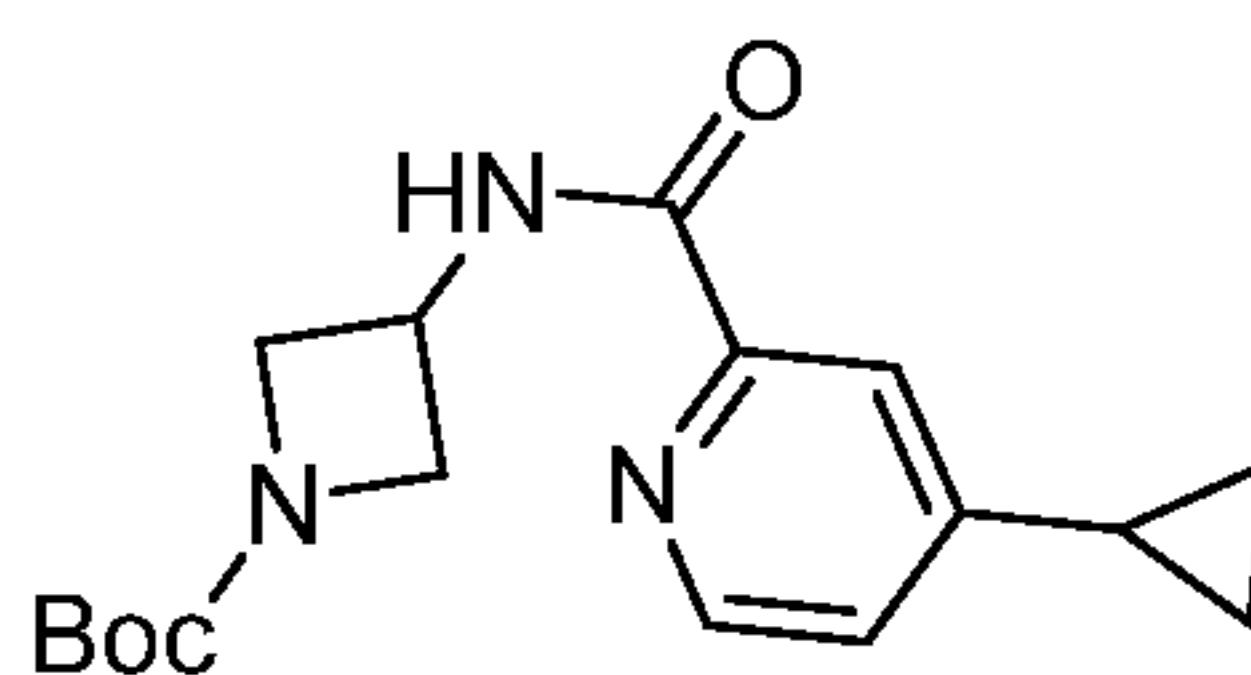


Step 1: Synthesis of tert-butyl 3-(4-bromopicolinamido)azetidine-1-carboxylate



[0373] To a solution of 4-bromopicolinic acid (10.0mmol, 2.02g), HATU (15.0mmol, 5.7g), HOAT (15.0mmol, 2.04g) and DIPEA (20.0mmol, 2.58g) in DMF (50ml) was added tert-butyl 3-aminoazetidine-1-carboxylate (10.0mmol, 1.72g) and stirred at r.t. overnight. Added ethyl acetate (300ml), washed with water (150ml X 6), dried over Na₂SO₄, concentrated and the residue was crystallized with ethyl acetate:petroleum ether=1:5 to give pale yellow powder (2.63g, 74%). ESI-LCMS (m/z): 356 [M+H]⁺.

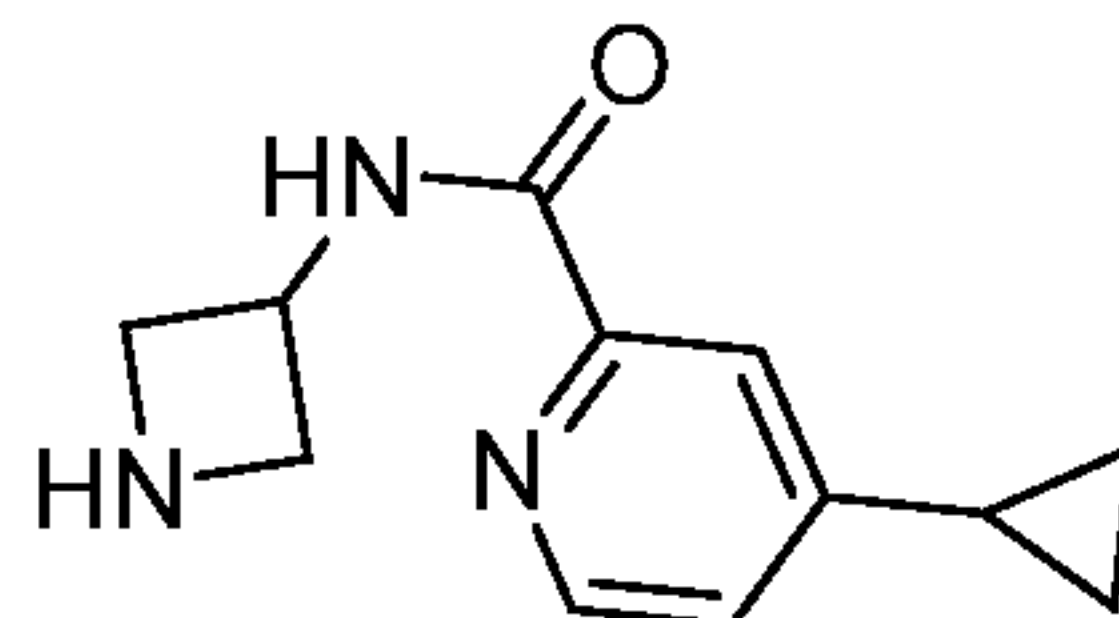
Step 2: Synthesis of tert-butyl 3-(4-cyclopropylpicolinamido)azetidine-1-carboxylate



[0374] To a solution of tert-butyl 3-(4-bromopicolinamido)azetidine-1-carboxylate (16.2mmol, 5.8g), cyclopropylboronic acid (32.4 mmol, 22.8g), K₃PO₄ (48.5mmol, 10.2g) in dioxane (50 mL) was added Pd(dppf)Cl₂ (1.61 mmol, 1.2 g). The mixture was degassed under reduced pressure while stirring and recharged with argon gas, this procedure was repeated for seven times and then heated to 100°C overnight. The solvent was removed and the residue was purified by column chromatography (eluant: ethyl

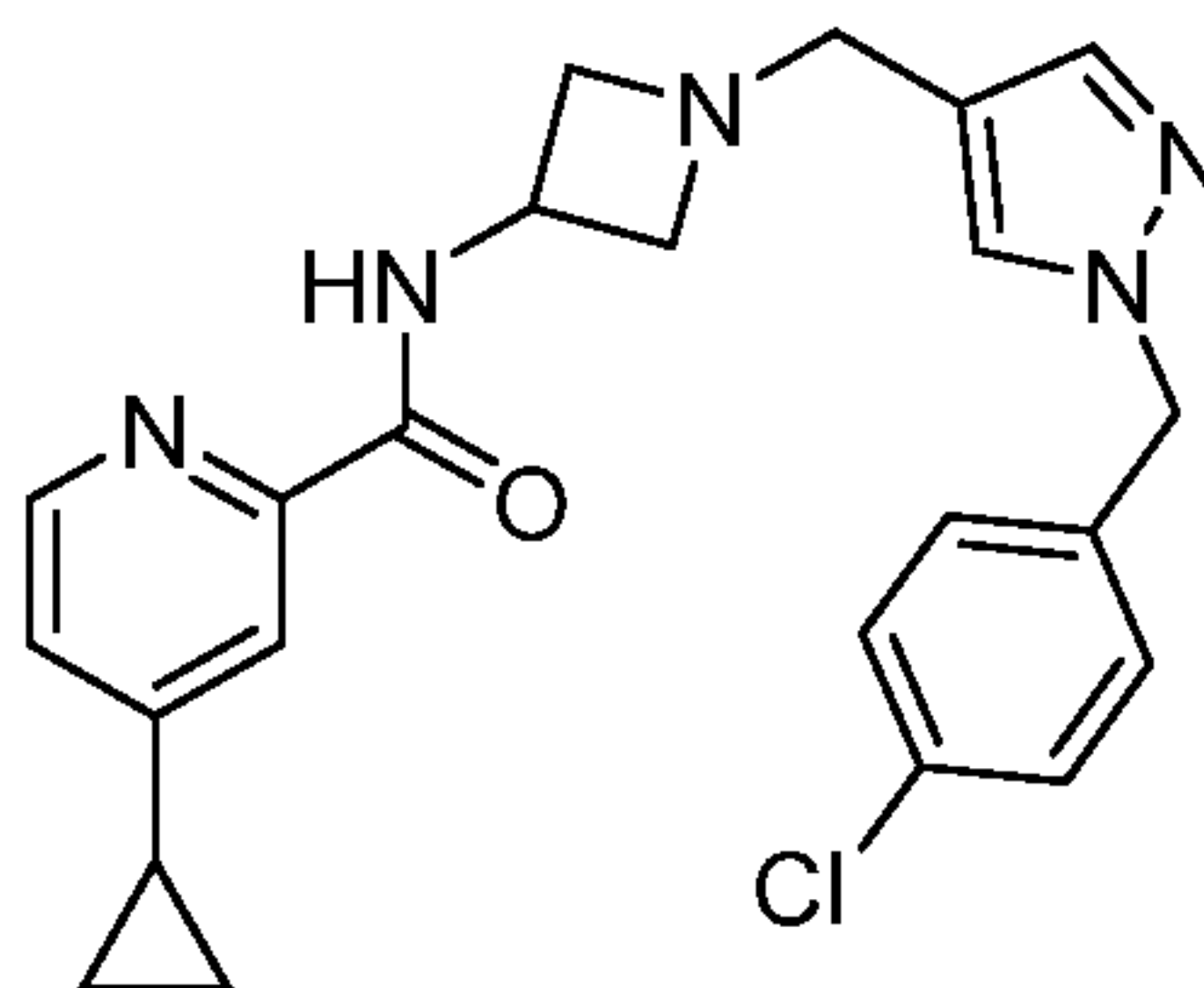
acetate:petroleum ether=1:3) to give tert-butyl 3-(4-cyclopropylpicolinamido)azetidine-1-carboxylate as a white solid (2.6 g, 50.5 %). ESI-LCMS (m/z): 318 [M+H]⁺.

Step 3: Synthesis of N-(azetidin-3-yl)-4-cyclopropylpicolinamide



[0375] tert-Butyl 3-(4-cyclopropylpicolinamido)azetidine-1-carboxylate (1.1 g, 3.46 mmol) in 3N HCl in MeOH (50 ml) was stirred at room temperature for 16h. LCMS showed the reaction was completed, the solvent was removed under reduced pressure, then NH₃ in MeOH (7N, 10ml) was added and concentrated. The crude product was purified by flash column chromatography (40g silica gel column, eluted with DCM:NH₃ in MeOH (7N)=10:1) to give the desired product N-(azetidin-3-yl)-4-cyclopropylpicolinamide (537mg, 71.5 %) as a white solid.

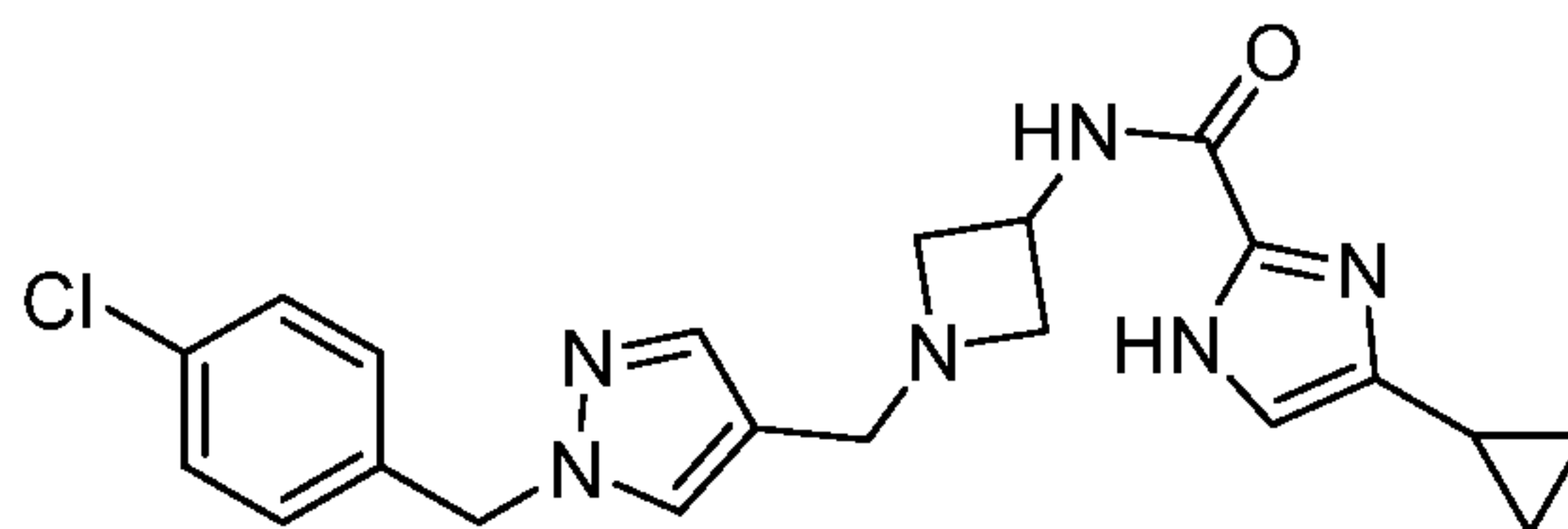
Step 4: Synthesis of N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-4-cyclopropylpicolinamide



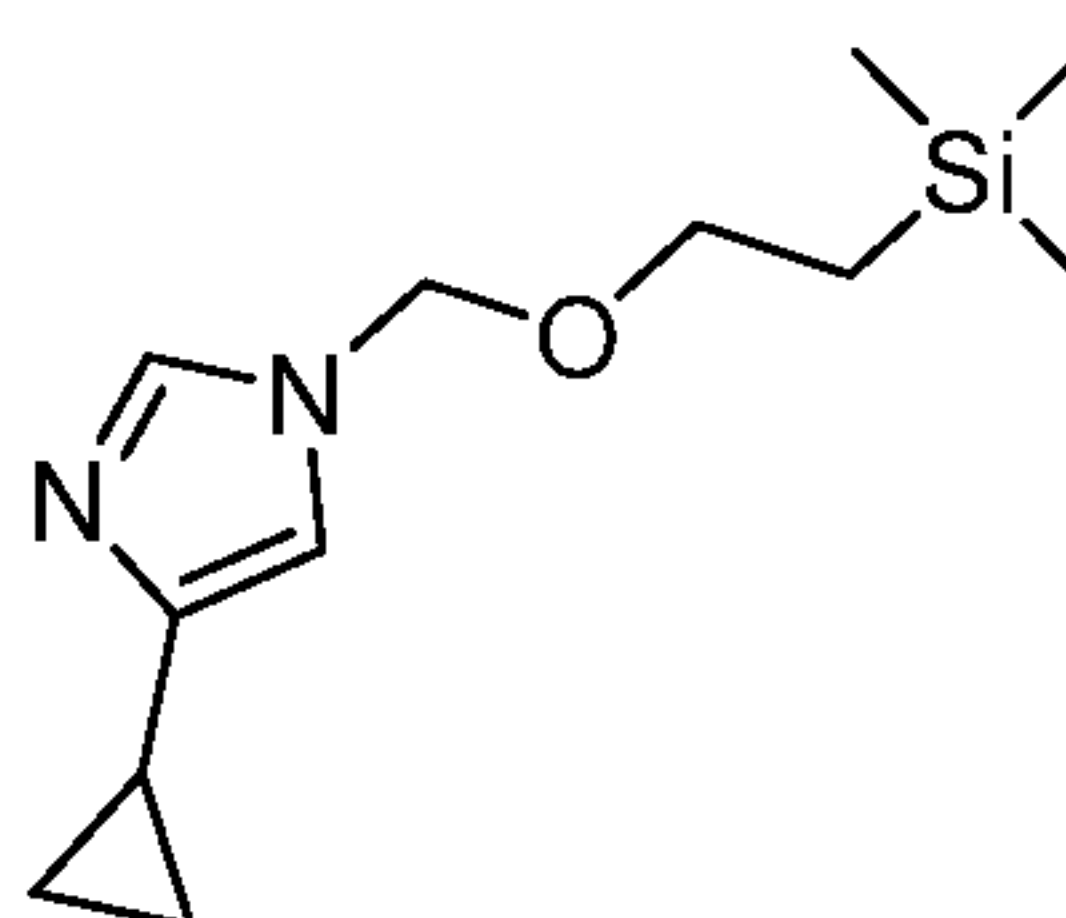
[0376] A mixture of N-(azetidin-3-yl)-4-cyclopropylpicolinamide (50 mg, 0.2301 mmol), 1-(4-chlorobenzyl)-1H-pyrazole-4-carbaldehyde (50.7 mg, 0.2301 mmol) and HOAc (34.5 mg, 0.6903 mmol) in MeOH (10ml) was stirred at r.t. for 16h. LCMS showed the reaction was completed, the solvent was removed under reduced pressure, NH₃ in MeOH (7N, 10ml) was added and concentrated, the crude product, which was purified by Prep-TLC (eluant: DCM : NH₃ in MeOH (7N) = 20:1) to give the desired product N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-4-cyclopropylpicolinamide (30mg, 30.9 %) as a colorless oil. ESI-LCMS (m/z): 422[M+H]⁺; ¹HNMR (400 MHz, CD₃OD) δ ppm: 8.44 (d, J=5.2 Hz, 1H), 7.76 (s, 1H), 7.68 (s, 1H), 7.51 (s, 1H), 7.35-7.32 (m, 2H), 7.28-7.26 (m, 1H), 7.20 (d, J=8.4 Hz, 2H), 5.32 (s, 2H), 4.67-4.63 (m, 1H), 3.73-3.69 (m, 2H), 3.62 (s, 2H), 3.26-3.22 (m, 2H), 2.05-2.01 (m, 1H), 1.20-1.15 (m, 2H), 0.91-0.87 (m, 2H).

EXAMPLE 31

Synthesis of N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-4-cyclopropyl-1H-imidazole-2-carboxamide (Cpd. No. 927)

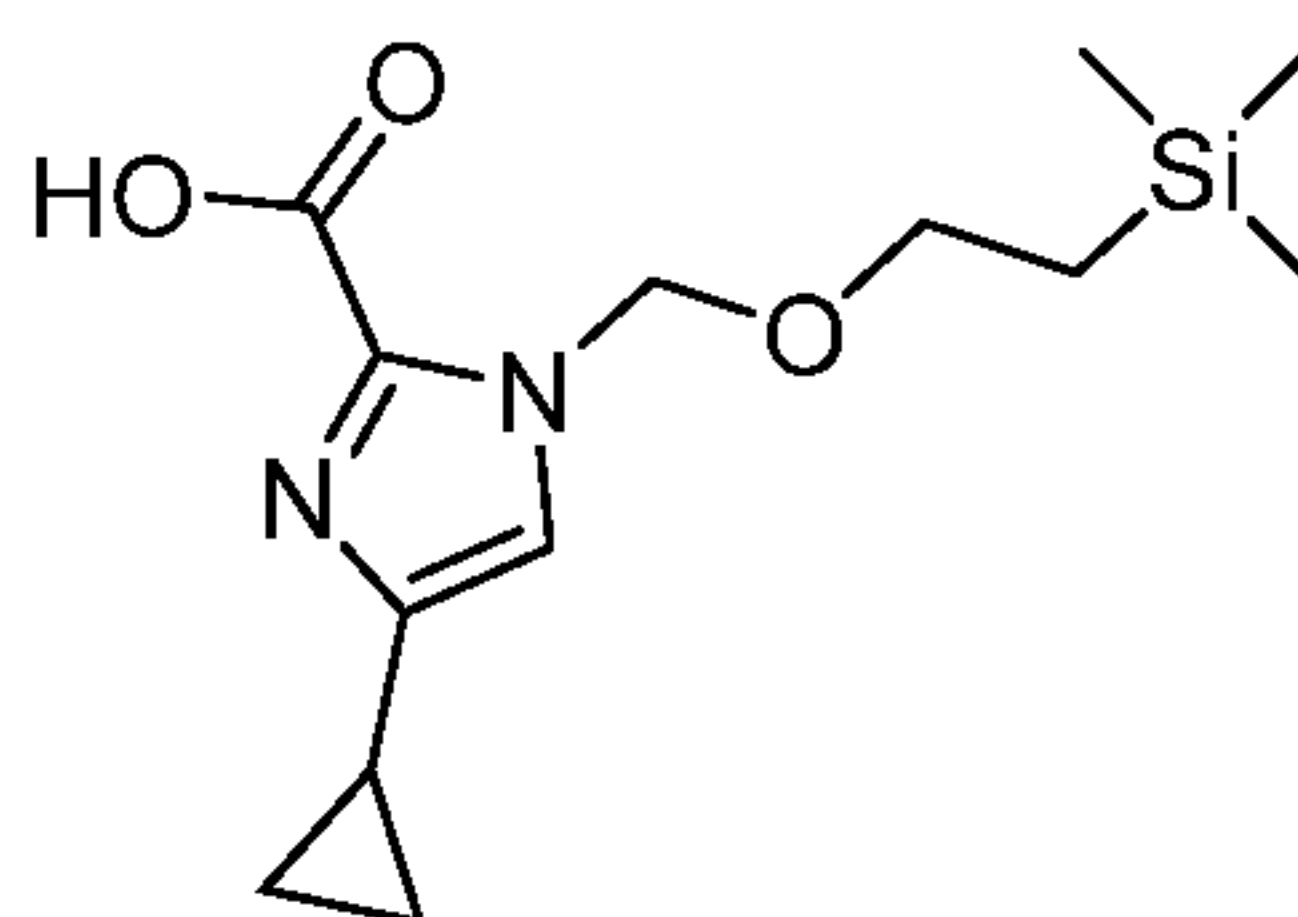


Step 1: Synthesis of 4-cyclopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole



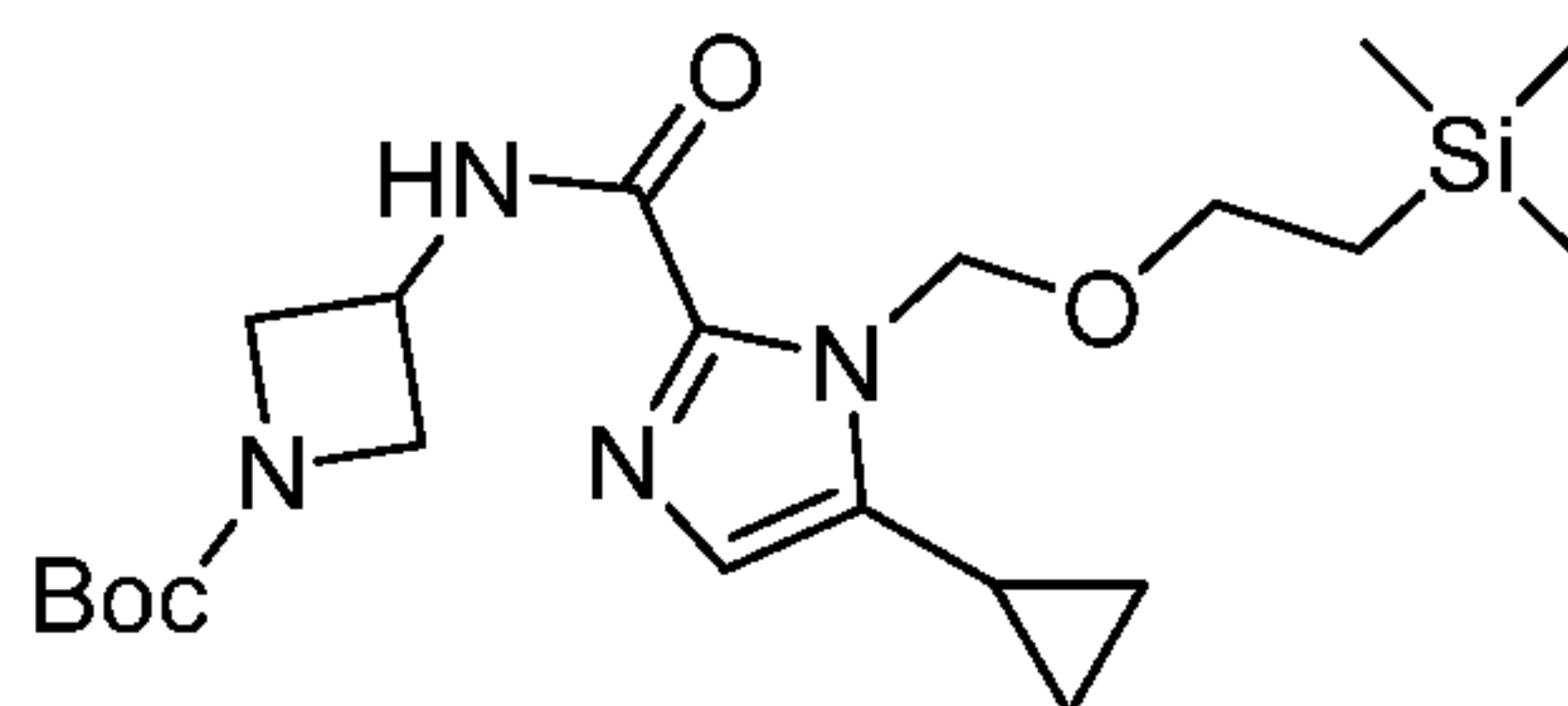
[0377] To a solution of 5-cyclopropyl-1H-imidazole (5.16 g, 47.7 mmol) in anhydrous THF (50 mL) was added NaH (2.85 g, 71.5 mmol) portion-wise at 0 °C under nitrogen atmosphere and the mixture was stirred 0 °C for 0.5 h. To the reaction mixture was added SEM-Cl (11.9 g, 71.5 mmol) dropwise at 0 °C under nitrogen atmosphere and the mixture was stirred at 0 °C for 2 h. The mixture was concentrated in vacuo and the residue was purified with column chromatograph on silica gel (petroleum ether:ethyl acetate=2:1) to afford 4-cyclopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (2.10g, 18.4%) as a yellow liquid. ESI-LCMS (m/z): 239[M+H]⁺.

Step 2: Synthesis of 4-cyclopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-2-carboxylic acid



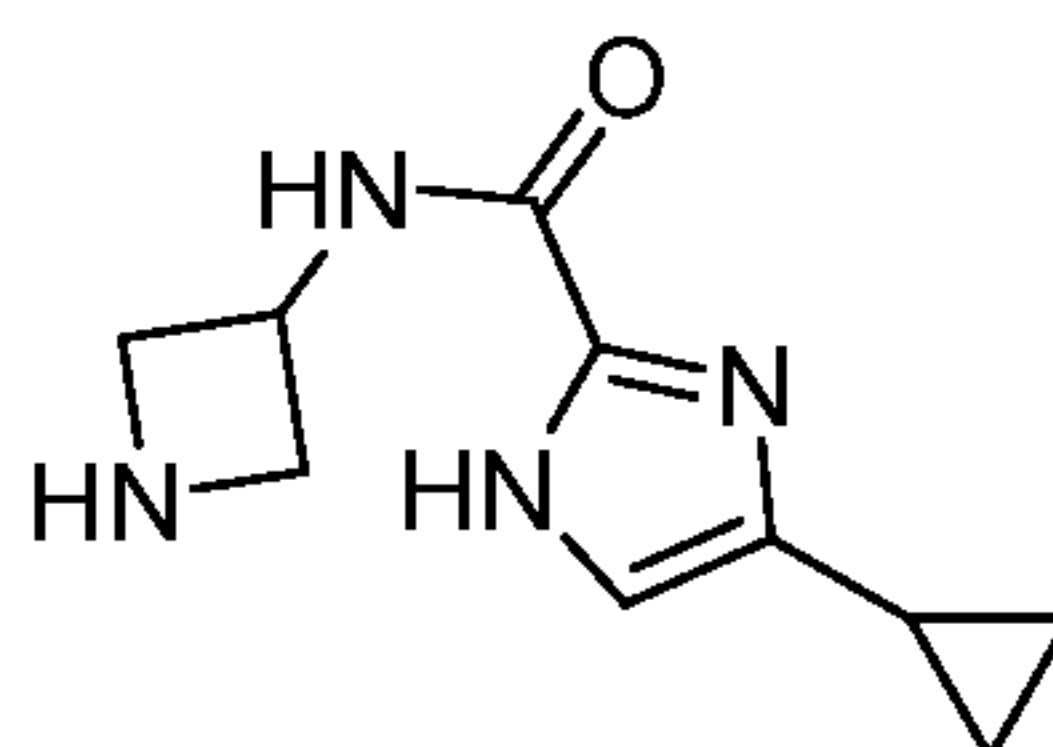
[0378] Into the stirred solution of 4-cyclopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (400 mg, 1.7 mmol) in THF (20 mL) was added BuLi (0.7 mL, 2.5 M) at -70 °C, the mixture was stirred at -70 °C for 1 h, then solid CO₂ was added at -70 °C, stirred for the next 1 h, acidified with HCl (1 M). Concentrated in vacuum to obtained desired product (350 mg, yellow oil, Y: 74%). ESI-LCMS (m/z): 283[M+H]⁺.

Step 3: Synthesis of tert-butyl 3-(4-cyclopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-2-carboxamido)azetidine-1-carboxylate



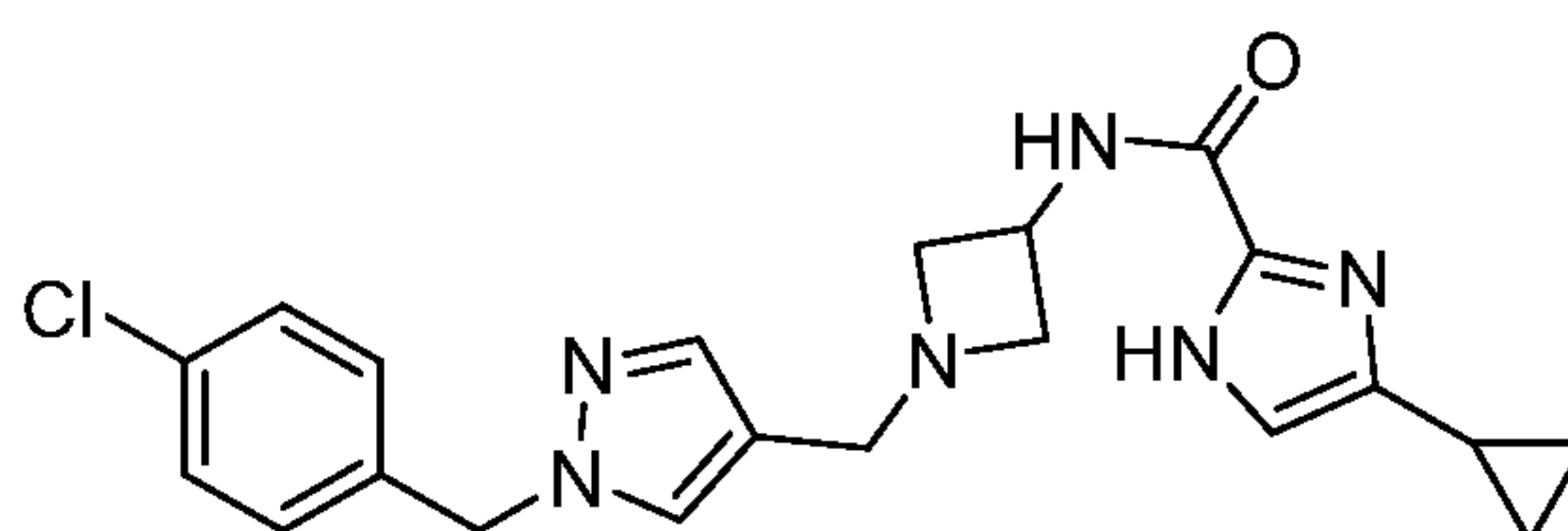
[0379] Into the stirred solution of 4-cyclopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-2-carboxylic acid (350 mg, 1.23 mmol), tert-butyl 3-aminoazetidine-1-carboxylate (316 mmol, 1.84 mmol) and HATU (700 mg, 1.84 mmol) in DMF (10 mL) was added DIPEA (478 mg, 3.7 mmol). The mixture was stirred at r.t. for 2 h. Concentrated in vacuum to remove the solvent, the residue was purified by Pre-TLC (petroleum ether:ethyl acetate 1:1) to afford tert-butyl 3-(4-cyclopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-2-carboxamido)azetidine-1-carboxylate as a colorless oil (200 mg, 37%). ESI-LCMS (m/z): 437[M+H]⁺.

Step 4: Synthesis of N-(azetidin-3-yl)-4-cyclopropyl-1H-imidazole-2-carboxamide



[0380] Into the stirred solution of tert-butyl 3-(4-cyclopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-2-carboxamido)azetidine-1-carboxylate (200 mg, 0.5 mmol) in DCM (10 mL) was added TFA (444 mg, 4.6 mmol). The mixture was stirred at r.t. for 2 h. Concentrated in vacuum to remove the solvent to obtain the residue, basified with saturated NaHCO₃, extracted with EtOAc (30 mL X 3), combined the organic layer, dried over Na₂SO₄, concentrated in vacuum to obtain the crude N-(azetidin-3-yl)-4-cyclopropyl-1H-imidazole-2-carboxamide, which was used without further purification (80 mg, brown oil, Y: 84%). ESI-LCMS (m/z): 207[M+H]⁺.

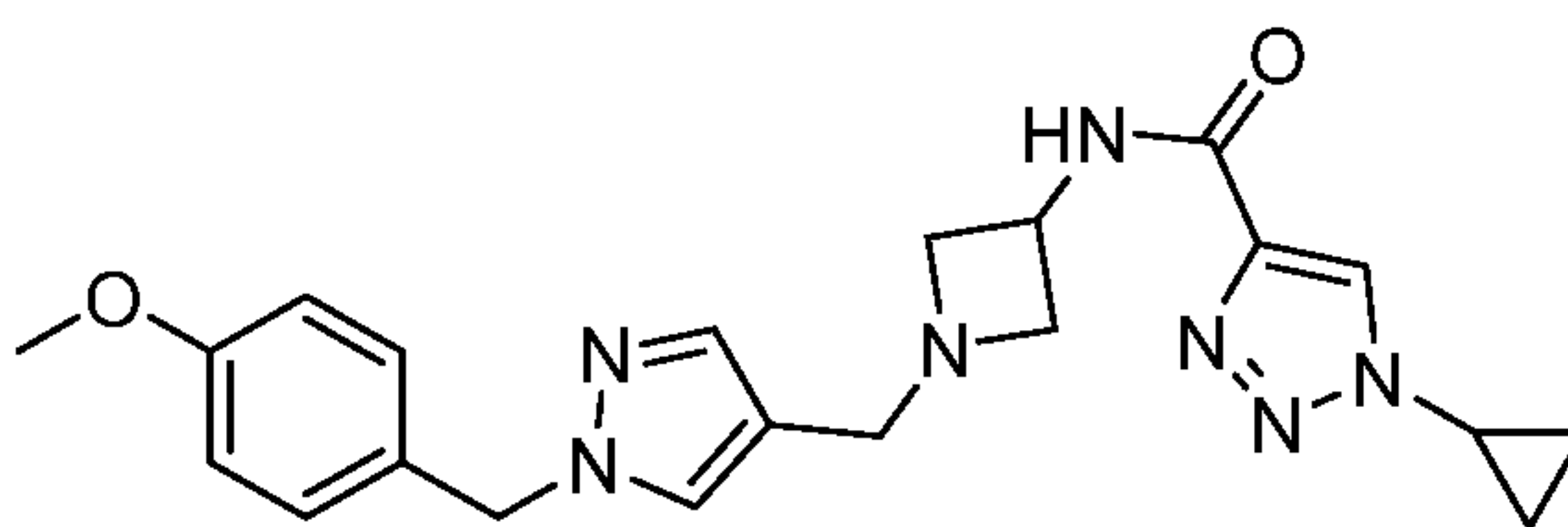
Step 5: Synthesis of N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-4-cyclopropyl-1H-imidazole-2-carboxamide



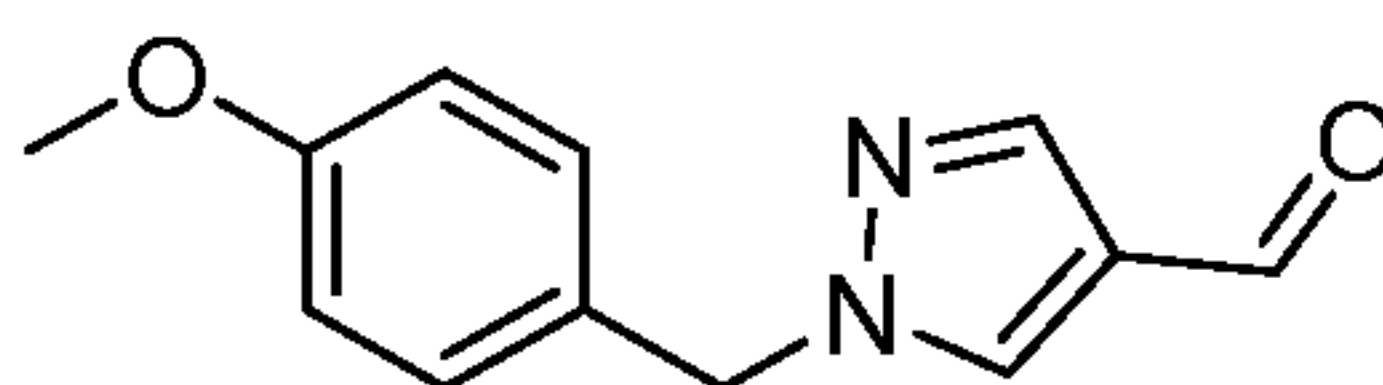
[0381] Into the stirred solution of N-(azetidin-3-yl)-4-cyclopropyl-1H-imidazole-2-carboxamide (400 mg, 1.9 mmol) and 1-(4-chlorobenzyl)-1H-pyrazole-4-carbaldehyde (425 mg, 1.9 mmol) in MeOH (20 mL) was added NaBH₃CN (600 mg, 9.6 mmol). The mixture was stirred at 60 °C for 20 h. The product was purified by reversed phase prep-HPLC (TFA, CH₃CN : H₂O = 5%-95%) to afford N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-4-cyclopropyl-1H-imidazole-2-carboxamide (49 mg, 6%). ESI-LCMS (m/z): 411[M+H]⁺; ¹HNMR (400 MHz, CD₃OD) δ ppm: 7.92 (s, 1H), 7.67 (s, 1H), 7.36-7.34 (m, 2H), 7.24 (d, J = 8.8 Hz, 2H), 6.91 (brs, 1H), 5.36 (s, 2H), 4.77-4.74 (m, 1H), 4.31-4.26 (m, 4H), 4.16-4.11 (m, 2H), 1.91-1.87 (m, 1H), 0.93-0.90 (m, 2H), 0.75-0.72 (m, 2H).

EXAMPLE 32

Synthesis of 1-cyclopropyl-N-(1-((1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide (Cpd. No. 932)

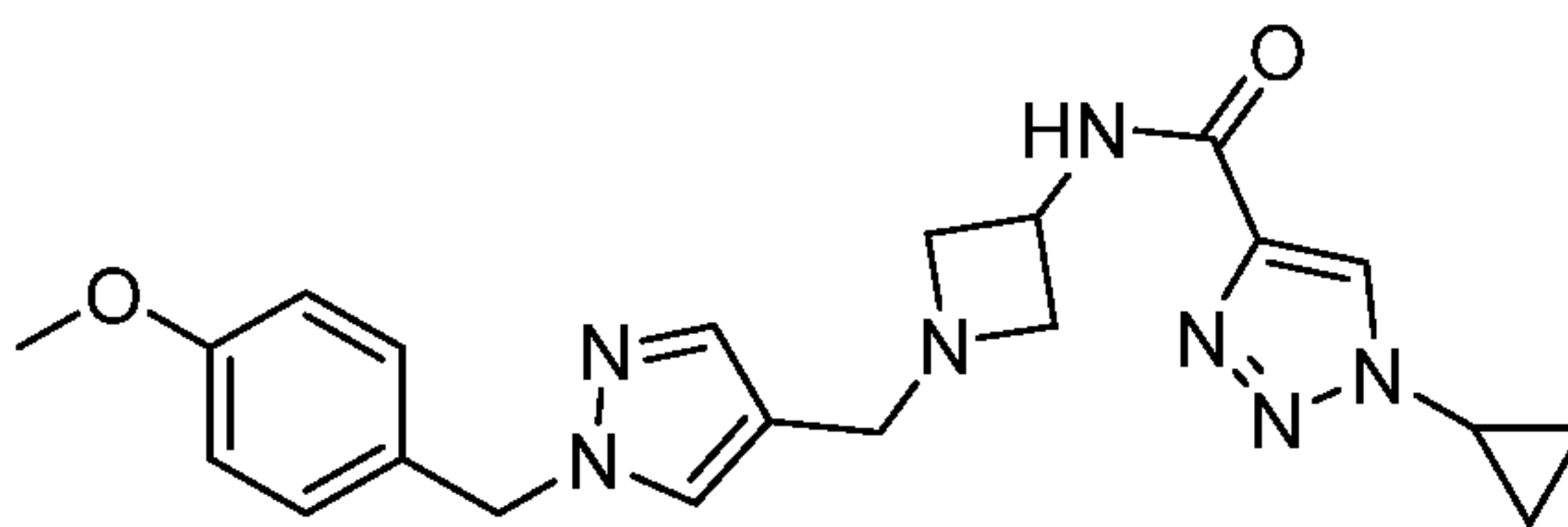


Step 1: Synthesis of 1-(4-methoxybenzyl)-1H-pyrazole-4-carbaldehyde



[0382] To a mixture of 1H-pyrazole-4-carbaldehyde (100 mg, 1.04 mmol) and 1-(chloromethyl)-4-methoxybenzene (162 mg, 1.04 mmol) in CH₃CN (6 mL) was added potassium carbonate (287 mg, 2.08 mmol), the resulting mixture was stirred at reflux for 1 h. The mixture was poured into water (20 mL) and extracted with EtOAc (3×20 mL). The organic layer was dried over Na₂SO₄ and concentrated to give 1-(4-methoxybenzyl)-1H-pyrazole-4-carbaldehyde (220 mg, 93.3 %) as a colorless oil. ESI-LCMS (m/z): 217[M+H]⁺.

Step 2: Synthesis of 1-cyclopropyl-N-(1-((1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide



[0383] To a mixture of N-(azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide (50 mg, 0.2412 mmol) and 1-(4-methoxybenzyl)-1H-pyrazole-4-carbaldehyde (62.5 mg, 0.2894 mmol) in methanol (5 mL) was added acetic acid (724 μ g, 0.01206 mmol), the mixture was stirred at r.t. for 15 min, then sodium cyanoborohydride (30.3 mg, 0.4824 mmol) was added, the resulting mixture was stirred at 40 °C overnight. The mixture was concentrated under reduced pressure. The residue was dissolved in aqueous solution of Na_2CO_3 and extracted with EtOAc (3 $\times$ 20 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by prep-TLC ($\text{CH}_2\text{Cl}_2/\text{NH}_3\cdot\text{MeOH}=20/1$) to give 1-cyclopropyl-N-(1-((1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide (53 mg, 53.9 %) as a white solid. ESI-LCMS (m/z): 408 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CD_3OD) δ ppm: 8.39 (s, 1H), 7.62 (s, 1H), 7.48 (s, 1H), 7.19 (d, J = 8.4 Hz, 2H), 6.90 d, J = 8.4 Hz, 2H), 5.24 (s, 2H), 4.64-4.62 (m, 1H), 3.99-3.98 (m, 1H), 3.79 (s, 3H), 3.73-3.69 (m, 2H), 3.63 (s, 2H), 3.27-3.23 (m, 2H), 1.28-1.22 (m, 4H).

EXAMPLE 33

SMYD3 Biochemical Assay

General Materials

[0384] S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), Tris, Tween20, dimethylsulfoxide (DMSO), bovine skin gelatin (BSG), and Tris(2-carboxyethyl)phosphine hydrochloride solution (TCEP) were purchased from Sigma-Aldrich at the highest level of purity possible. ^3H -SAM was purchase from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. 384-well opaque white OptiPlates and SPA beads (Perkin Elmer, catalog # RPNQ0013) were purchased from PerkinElmer.

Substrates

[0385] N-terminally GST-tagged MEKK2 (MAP3K2) protein corresponding to reference sequence AAF63496.3 was purchased from Life Technologies (catalog # PV4010). This

protein was expressed in High Five insect cells and purified to >85 % purity. Protein identity was confirmed by MS/MS analysis after proteolytic digestion. The protein sequence used was:

MAPILGYWKIKGLVQPTRLLEYLEEKYEEHLYERDEGDKWRNK
 KFELGLEFPNLPYYIDGDVKLTQSMAIIRYIADKHNMLGGCPKERA
 EISMLEGAVLDIRYGVSR IAYSKDFETLKVDFLSKLPEMLKMFEDR
 LCHKTYLNGDHVTHPDFMLYDALDVVLYMDPMCLDAFPKLVCF
 KKRIEAIPQIDKYLKSSKYIAWPLQG WQATFGGGDHPPKSDLVPRH
 NQTSLYKKAGTMDDQQALNSIMQDLAVLHKASRPALSLQETRKA
 KSSSPKKQNDVRVKFEHRGEKRILQFPRPVKLEDLRSKAKIAFGQS
 MDLHYTNNELVIPLTTQDDLDKALELLDRSIHMKSLKILLVINGST
 QATNLEPLPSLEDLDNTVFGAERKKRLSIIGPTSRDRSSPPPGYIPDE
 LHQVARNGSFTSINSEGEFIPESMEQMLDPLSLSSPENSGSGSCPSL
 DSPLDGESYPKSRMPRAQSYPDNHQEFSDYDNPIFEKFGKGGTYPR
 RYHVSYYHHQEYNDGRKTFPRARRTQGNQLTSPVSFSPTDHSLSSTSS
 GSSIFTPEYDDSRIRRRGSDIDNPTLTVMDISPPSRSPRAPTNWRLG
 KLLGQGAFGRVYLCYDVDTGRELAVKQVQFDPDSPETSKEVNAL
 ECEIQLLLKNLLHERIVQYYGCLRDPQEKTLSIFMEYMPGGSIKDQL
 KAYGALTENVTRKYTRQILEGVHYLHSNMIVHRDIKGANILRDST
 GNVKLGDFGASKRLQTICLSGTGMKSVTGTPYWMSPEVISGQGYG
 RKADIWSVACTVVEMLTEKPPWAEFEAMAAIFKIATQPTNPKLPP
 HVSDYTRDFLKRIFVEAKLRPSADELLRHMFVHYH.

(SEQ ID No. 1).

Molecular Biology

[0386] Full-length human SMYD3 isoform 1 (BAB86333) was inserted into a modified pET21b plasmid containing a His6 tag and TEV and SUMO cleavage sites. Because two common variants of SMYD3 exist in the population, site directed mutagenesis was subsequently performed to change amino acid 13 from an asparagine to a lysine, resulting in plasmid pEPZ533. A lysine at position 13 conforms to the more commonly occurring sequence (NP_001161212).

Protein Expression

[0387] *E. coli* (BL21 codonplus RIL strain, Stratagene) were transformed with plasmid pEPZ553 by mixing competent cells and plasmid DNA and incubating on ice for 30 minutes followed by heat shock at 42 °C for 1 minute and cooling on ice for 2 minutes. Transformed cells were grown and selected on LB agar with 100 µg/mL ampicillin and 17 µg/mL chloramphenicol at 37 °C overnight. A single clone was used to inoculate 200 mL of LB medium with 100 µg/mL ampicillin and 17 µg/mL chloramphenicol and incubated at 37 °C on an orbital shaker at 180 rpm. Once in log growth, the culture was diluted 1:100 into 2 L of LB medium and grown until OD₆₀₀ was about 0.3 after which the culture was incubated at 15 °C and 160 rpm. Once OD₆₀₀ reached about 0.4, IPTG was added to a final concentration of 0.1 mM and the cells were grown overnight at 15 °C and 160 rpm. Cells were harvested by centrifugation at 8000 rpm, for 4 minutes at 4 °C and stored at -80 °C for purification.

Protein Purification

[0388] Expressed full-length human His-tagged SMYD3 protein was purified from cell paste by Nickel affinity chromatography after equilibration of the resin with Buffer A (25 mM Tris, 200 mM NaCl, 5% glycerol, 5 mM β-mercaptoethanol, pH7.8). The column was washed with Buffer B (Buffer A plus 20 mM imidazole) and His-tagged SMYD3 was eluted with Buffer C (Buffer A plus 300 mM imidazole). The His tag, TEV and SUMO cleavage sites were removed generating native SMYD3 by addition of ULP1 protein at a ratio of 1:200 (ULP1:SMYD3). Imidazole was removed by dialysis overnight in Buffer A. The dialyzed solution was applied to a second Nickel column and the native SMYD3 protein was collected from the column flow-through. The flow-through was dialyzed in Buffer D (25 mM Tris, 5% glycerol, 5 mM β-mercaptoethanol, 50 mM NaCl, pH7.8) and ULP1 was removed using a Q sepharose fast flow column. SMYD3 was eluted in Buffer A and further purified using an S200 size-exclusion column equilibrated with Buffer A. SMYD3 was concentrated to 2 mg/mL with a final purity of 89%.

Predicted Translation:

[0389] SMYD3 (Q9H7B4)
 MEPLKVEKFATAKRGNGLRVTPLRPGELLFRSDPLAYTVCKGSR
 GVVCDRCLLGKEKLMRCSQCRVAKYCSAKCQKKAWPDHKRECK
 CLKSCCKPRYPDSVRLGRVVFVKLMDGAPSESEKLYSFYDLESNIN

KLTEDEKKEGLRQLVMTFQHFMREEIQDASQLPPAFDLFEAFKVIC
 NSFTICNAEMQEVGVGLYPSISLLNHSCDPNCSIVFNGPHLLLRAV
 RDIEVGEELTICYLDMLMTSEERRKQLRDQYCFECDCFRQCQTQDK
 DADMLTGDEQVWKEVQESLKKIEELKAHWKWEQVLAMCQAISS
 NSERLPDINIYQLKVLDCAMDACINLGLLEEALFYGTRTMEPYRIFF
 PGSHPVVRGVQVMKVGKLQLHQGMFPQAMKNLRLAFDIMRVTHG
 REHSLIEDLILLLEECDANIRAS. (SEQ ID No. 2).

General Procedure for SMYD3 Enzyme Assays on MEKK2 protein substrate

[0390] The assays were all performed in a buffer consisting of 25 mM Tris-Cl pH 8.0, 1 mM TCEP, 0.005% BSG, and 0.005% Tween 20, prepared on the day of use. Compounds in 100% DMSO (1ul) were spotted into a 384-well white opaque OptiPlate using a Bravo automated liquid handling platform outfitted with a 384-channel head (Agilent Technologies). DMSO (1ul) was added to Columns 11, 12, 23, 24, rows A-H for the maximum signal control and 1ul of SAH, a known product and inhibitor of SMYD3, was added to columns 11, 12, 23, 24, rows I-P for the minimum signal control. A cocktail (40ul) containing the SMYD3 enzyme was added by Multidrop Combi (Thermo-Fisher). The compounds were allowed to incubate with SMYD3 for 30 min at room temperature, then a cocktail (10ul) containing SAM and MEKK2 was added to initiate the reaction (final volume = 51ul). The final concentrations of the components were as follows: SMYD3 was 0.4 nM, ³H-SAM was 8 nM, MEKK2 was 12 nM, SAH in the minimum signal control wells was 1 mM, and the DMSO concentration was 2%. The assays were stopped by the addition of non-radiolabeled SAM (10ul) to a final concentration of 100 uM, which dilutes the ³H-SAM to a level where its incorporation into MEKK2 is no longer detectable. Radiolabeled MEKK2 was detected using a scintillation proximity assay (SPA). 10 uL of a 10 mg/mL solution of SPA beads in 0.5 M citric acid was added and the plates centrifuged at 600 rpm for 1 min to precipitate the radiolabeled MEKK2 onto the SPA beads. The plates were then read in a PerkinElmer TopCount plate reader to measure the quantity of ³H-labeled MEKK2 as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

% inhibition calculation

$$\% \text{ inh} = 100 - \left(\frac{\text{dpm}_{\text{cmpd}} - \text{dpm}_{\text{min}}}{\text{dpm}_{\text{max}} - \text{dpm}_{\text{min}}} \right) \times 100$$

[0391] Where dpm = disintegrations per minute, cmpd = signal in assay well, and min and max are the respective minimum and maximum signal controls.

Four-parameter IC50 fit

$$Y = \text{Bottom} + \frac{(\text{Top} - \text{Bottom})}{\left(1 + \left(\frac{X}{\text{IC}_{50}}\right)^{\text{Hill Coefficient}}\right)}$$

[0392] Where top and bottom are the normally allowed to float, but may be fixed at 100 or 0 respectively in a 3-parameter fit. The Hill Coefficient normally allowed to float but may also be fixed at 1 in a 3-parameter fit. Y is the % inhibition and X is the compound concentration.

[0393] SMYD3 biochemical assay data for representative Compounds of the Disclosure are presented in Tables 1A and 3A in the column titled "SMYD3 Biochem IC₅₀ (μM)."

EXAMPLE 34

SMYD3 Cell Assay

Trimethyl-MEKK2-In-Cell Western Assay

[0394] 293T/17 adherent cells were purchased from ATCC (American Type Culture Collection), Manassas, VA, USA. MEM/Glutamax medium, Optimem Reduced Serum medium, penicillin-streptomycin, 0.05% trypsin and 1x D-PBS were purchased from Life Technologies, Grand Island, NY, USA. PBS-10X was purchased from Ambion, Life Technologies, Grand Island, New York, USA. PBS with Tween 20 (PBST (10x)) was purchased from KPL, Gaithersburg, Maryland, USA. Tet System FBS- approved FBS US Source was purchased from Clontech, Mountain View, California, USA. Odyssey blocking buffer, 800CW goat anti-rabbit IgG (H+L) antibody, 680CW Goat anti-mouse IgG (H+L) and Licor Odyssey infrared scanner were purchased from Licor Biosciences, Lincoln, NE, USA. Tri-methyl-Lysine [A260]-MEKK2 antibody, MEKK2 and SMYD3 plasmids were made at Epizyme. Anti-flag monoclonal mouse antibody was purchased from Sigma, St. Louis, MO, USA. Methanol was purchased from VWR, Franklin, MA, USA. 10% Tween 20 was purchased from KPL, Inc., Gaithersburg, Maryland, USA. Eugene was purchased from Promega, Madison, WI, USA. The Biotek ELx405 was

purchased from BioTek, Winooski, Vermont, USA. The multidrop combi was purchased from Thermo Scientific, Waltham, Massachusetts, USA.

[0395] 293T/17 adherent cells were maintained in growth medium (MEM/Glutamax medium supplemented with 10% v/v Tet System FBS and cultured at 37 °C under 5% CO₂.

Cell treatment, In Cell Western (ICW) for detection of trimethyl-lysine-MEKK2 and MEKK2.

[0396] 293T/17 cells were seeded in assay medium at a concentration of 33,333 cells per cm² in 30 mL medium per T150 flask and incubated at 37 °C under 5% CO₂. Plasmids were prepared for delivery to cells by first mixing 1350 µL Opti-MEM with Fugene (81 µL) in a sterile Eppendorf and incubated for five minutes at room temperature (RT). MEKK2-flag (13.6 ug/T150) MEKK2 p3XFlag-CMV-14 with C-3XFlag and SMYD3 (0.151 ug/T150) SMYD3 p3XFlag-CMV-14 without C-3XFlag plasmids were aliquotted to a 1.7 mL sterile microfuge tube. The gene ID for MEKK2 and SMYD3 is NM_006609.3 and Q9H7B4, respectively. Entire volume of Opti-MEM/Fugene mixture was then added to a microfuge tube containing DNA plasmid, mixed and then incubated x 15 minutes at RT. The medium on the 293T/17 cells was refreshed, and the DNA/Fugene complex is added aseptically to each flask, rocked gently, and incubated at 37 C for 5 hours. Medium was then removed, and cells were washed once with PBS in the flask. Trypsin 0.05% (3mL) was added and cells incubated for three minutes. Room temperature MEM+10% Tet system FBS was added and cells were mixed gently, and counted using the Vi-cell. Cells were seeded at 100,000 cells/mL in 50 µL MEM/10%Tet FBS/Pen/Strep to a 384 well black/clear poly-D-lysine coated plate containing test agent diluted in DMSO. The final top concentration of test compound was 40 µM. The total concentration of DMSO did not exceed 0.2% (v/v). Plates were incubated x 30 minutes at RT in low-airflow area, followed by incubation at 37 °C under 5% CO₂ for 24 hours. Medium was aspirated from all wells of assay plates prior to fixation and permeabilization with ice cold (-20 °C) methanol (90 µL/well) for ten minutes. Plates were rinsed with PBS three times on BioTek ELx405. PBS was removed with a final aspiration, and Odyssey blocking buffer (50 µL/well) was added to each well and incubated for one hour at RT. Primary antibody solution was prepared (anti-trimethyl-MEKK2 at 1:600 dilution plus mouse anti-flag antibody at 1:10,000

dilution in diluent (Odyssey Blocking buffer + 0.1% Tween 20)) and 20 μ L per well was dispensed using the Multidrop Combi. Assay plates were then sealed with foil, and incubated overnight at 4° C. Plates were washed five times with PBS-Tween (1X) on Biotek ELx405 and blotted on paper towel to remove excess reagent. Detection antibody solution (IRDye 800 CW goat anti-rabbit IgG diluted 1:400 in diluent (Odyssey Blocking buffer + 0.1% Tween 20), plus IRDye 680CW goat anti-mouse IgG at 1:500 in diluent (Odyssey Blocking buffer + 0.1% Tween 20) was added (20 μ L/well) and incubated in dark for one hour at RT. Plates were then washed four times with PBS-T (1X) on ELx405. A final rinse with water was performed (115 μ L/well x three washes on the ELx405). Plates were then centrifuged upside down, on paper towel, at 200 x g to remove excess reagent. Plates were left to dry in dark for one hour. The Odyssey Imager was used to measure the integrated intensity of 700 and 800 wavelengths at resolution of 84 μ m, medium quality, focus offset 4.0, 700 channel intensity = 3.5 to measure the MEKK2-flag signal, 800 channel intensity = 5 to measure the Trimethyl-MEKK2 signal of each well.

Calculations:

[0397] First, the ratio for each well was determined by:

$$\left(\frac{\text{Trimethyl MEKK2 800nm value}}{\text{flag tagged MEKK2 700nm value}} \right)$$

[0398] Each plate included fourteen control wells of DMSO only treatment (Minimum Inhibition) as well as fourteen control wells for maximum inhibition (Background). The average of the ratio values for each control type was calculated and used to determine the percent inhibition for each test well in the plate. Reference compound was serially diluted two-fold in DMSO for a total of nine test concentrations, beginning at 40 μ M. Percent inhibition was calculated (below).

$$\text{Percent Inhibition} = 100 - \left(\left(\frac{(\text{Individual Test Sample Ratio}) - (\text{Background Avg Ratio})}{(\text{Minimum Inhibition Ratio}) - (\text{Background Average Ratio})} \right) * 100 \right)$$

[0399] Non-linear regression curves were generated to calculate the IC₅₀ and dose-response relationship using triplicate wells per concentration of compound.

[0400] SMYD3 cell assay data for representative Compounds of the Disclosure are presented in Tables 1A and 3A in the column titled "SMYD3 Cell IC₅₀ (μ M)."

EXAMPLE 35

SMYD2 Biochemical Assay

General Materials

[0401] S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), bicine, Tween20, dimethylsulfoxide (DMSO), bovine skin gelatin (BSG), and Tris(2-carboxyethyl)phosphine hydrochloride (TCEP) were purchased from Sigma-Aldrich at the highest level of purity possible. ³H-SAM was purchase from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. 384-well streptavidin Flashplates were purchased from PerkinElmer.

Substrates

[0402] Peptide was synthesized with a N-terminal linker-affinity tag motif and a C-terminal amide cap by 21st Century Biochemicals. The peptide was high high-performance liquid chromatography (HPLC) purified to greater than 95% purity and confirmed by liquid chromatography mass spectrometry (LC-MS). The sequence was ARTKQTARKSTGGKAPRKQLATKAARKSA(K-Biot)-amide. (SEQ ID NO: 3)

Production of Recombinant SMYD2 Enzymes for Biochemical Enzyme Activity Assays

[0403] Full length SMYD2 (NP_064582.2) was cloned into a pFastbac-Htb-lic vector with an N-terminal His6 *tag* and *FLAG tag*, preceded by a *TEV* protease *cleavage* site. The protein was expressed in Sf9 insect cells. Cells were resuspended in lysis buffer (25 mM HEPES-NaOH, pH 7.5, 200 mM NaCl, 5% glycerol, and 5 mM β-ME) and lysed by sonication. The protein was purified by Ni-NTA (Qiagen), followed by TEV cleavage to remove the His6 tag, subtractive Ni-NTA (Qiagen), and gel filtration chromatography using an S200 column (GE Healthcare). Purified protein was stored in 20 mM Tris-HCl, pH 8.0, 100 mM NaCl, and 1 mM TCEP.

General Procedure for SMYD2 Enzyme Assays on Peptide Substrates

[0404] The assays were all performed in a buffer consisting of 20mM Bicine (pH=7.6), 1mM TCEP, 0.005% Bovine Skin Gelatin, and 0.002% Tween20, prepared on the day of use. Compounds in 100% DMSO (1ul) were spotted into a polypropylene 384-well V-bottom plates (Greiner) using a Platamate Plus outfitted with a 384-channel head

(Thermo Scientific). DMSO (1ul) was added to Columns 11, 12, 23, 24, rows A-H for the maximum signal control and 1ul of SAH, a known product and inhibitor of SMYD2, was added to columns 11, 12, 23, 24, rows I-P for the minimum signal control. A cocktail (40ul) containing the SMYD2 enzyme was added by Multidrop Combi (Thermo-Fisher). The compounds were allowed to incubate with SMYD2 for 30 min at room temperature, then a cocktail (10ul) containing ^3H -SAM and peptide was added to initiate the reaction (final volume = 51ul). The final concentrations of the components were as follows: SMYD2 was 1.5nM, ^3H -SAM was 10nM, and peptide was 60nM, SAH in the minimum signal control wells was 1000uM, and the DMSO concentration was 2%. The assays were stopped by the addition of non-radioactive SAM (10ul) to a final concentration of 600uM, which dilutes the ^3H -SAM to a level where its incorporation into the peptide substrate is no longer detectable. 50ul of the reaction in the 384-well polypropylene plate was then transferred to a 384-well Flashplate and the biotinylated peptides were allowed to bind to the streptavidin surface for at least 1 hour before being washed three times with 0.1%Tween20 in a Biotek ELx405 plate washer. The plates were then read in a PerkinElmer TopCount plate reader to measure the quantity of ^3H -labeled peptide bound to the Flashplate surface, measured as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

% inhibition calculation

$$\% \text{ inh} = 100 - \left(\frac{\text{dpm}_{\text{compd}} - \text{dpm}_{\text{min}}}{\text{dpm}_{\text{max}} - \text{dpm}_{\text{min}}} \right) \times 100$$

[0405] Where dpm = disintegrations per minute, compd = signal in assay well, and min and max are the respective minimum and maximum signal controls.

Four-parameter IC50 fit

$$\% \text{ inhibition} = \text{Bottom} + \frac{\text{Top} - \text{Bottom}}{(1 + (\text{IC}_{50}/[I])^{\text{Hill slope}/\text{HillSlope}})}$$

[0406] Where top and bottom are the normally allowed to float, but may be fixed at 100 or 0 respectively in a 3-parameter fit. The Hill Coefficient normally allowed to float but may also be fixed at 1 in a 3-parameter fit. I is the compound concentration.

[0407] SMYD2 biochemical assay data for representative Compounds of the Disclosure are presented in Tables 4A and 6A in the column titled "SMYD2 Biochem IC₅₀ (μM)."

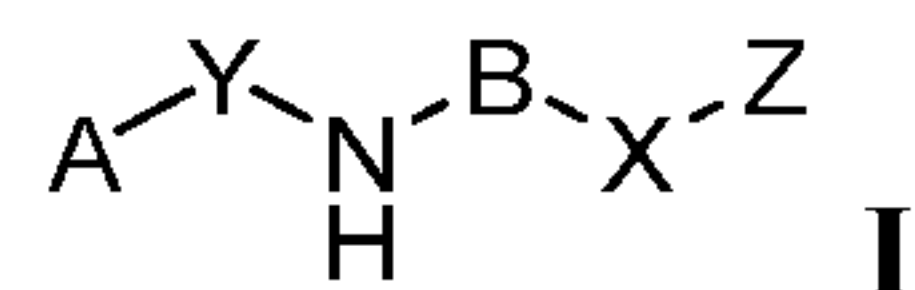
[0408] Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the invention or any embodiment thereof.

[0409] Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

[0410] All patents and publications cited herein are fully incorporated by reference herein in their entirety.

What is Claimed Is:

1. A compound having Formula I:



or a pharmaceutically acceptable salt or hydrate thereof,
wherein:

A is selected from the group consisting of 1,2,3-triazolyl, 1,2,4-triazolyl, 1-imidazolyl, 1-isoquinolyl, 1-pyrazolyl, 2-(1,2,3,4-tetrahydroquinolyl), 2-benzo[d]imidazolyl, 2-benzo[d]thiazolyl, 2-chromenyl-4-one, 2-furanyl, 2-imidazo[1,2-b]pyridazinyl, 2-imidazolyl, 2-indolyl, 2-naphthalenyl, 2-pyrazinyl, 2-pyridyl, 2-pyrimidinyl, 2-pyrrolidinyl, 2-pyrrolyl, 2-quinolyl, 2-quinoxalyl, 2-thiazolo[5,4-c]pyridinyl, 2-thiazolyl, 2-thiophenyl, 3-(1,2,3,4-tetrahydroisoquinoline), 3-(1,2,4-oxadiazolyl), 3-imidazo[1,2-a]pyrimidinyl, 3-indazolyl, 3-indolyl, 3-isothiazolyl, 3-pyrazolyl, 3-pyridazinyl, 3-pyridinyl-2-one, 3-pyridyl, 3-pyrrolo[3,2-b]pyridinyl, 3-quinolyl, 4-(2,2-difluorobenzo[d][1,3]dioxolyl), 4-cyclohexanyl-1-amine, 4-imidazolyl, 4-indolyl-2-one, 4-indolyl, 4-isothiazolyl, 4-oxazolyl, 4-piperidinyl, 4-pyrazolyl, 4-pyridyl, 4-quinolyl, 5-(1,3-dihydro-2H-benzo[d]imidazolyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-b]pyridinyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-c]pyridinyl-2-one), 5-(2,2-difluorobenzo[d][1,3]dioxolyl), 5-(2,4-dihydro-3H-1,2,4-triazolyl-3-one), 5-4H-furo[3,2-b]pyrrolyl, 5-benzo[c][1,2,5]oxadiazolyl, 5-benzo[d][1,3]dioxolyl, 5-benzo[d]oxazolyl-2(3H)-one, 5-bicyclo[2.2.1]heptyl-2-ene, 5-indolyl-2,3-dione, 5-indolyl-2-one, 5-indolyl, 5-isoindolyl-1-one, 5-isoxazolyl, 5-pyrazolo[3,4-c]pyridinyl, 5-pyrazolyl, 5-pyrimidinyl, 5-thiazolyl, 6-(1,2,3,4-tetrahydronaphthalenyl), 6-(3,4-dihydroquinolyl-2(1H)-one), 6-(3,4-dihydroquinoxalyl-2(1H)-one), 6-(4,5-dihydropyridazinyl-3(2H)-one), 6-benzo[b][1,4]oxazinyl-3-one, 6-benzo[d]imidazolyl, 6-benzo[d]oxazolyl-2(3H)-one, 6-benzo[d]thiazolyl, 6-chromenyl-2-one, 6-imidazo[2,1-b]thiazole, 6-indazolyl, 6-indolyl-2-one, 6-indolyl, 6-isoquinolyl, 6-quinolyl, 6-quinoxalyl, 6-quinoxalyl-2(1H)-one, 7-(3,4-dihydroquinolyl-2(1H)-one), 7-(3,4-dihydroquinoxalin-2(1H)-one), 7-benzo[b][1,4]oxazinyl-3-one, 7-indolyl-2-one, 7-quinolyl, 8-benzo[b][1,4]oxazinyl-3-one, cyclopropanyl, phenyl, 4-(prop-1-en-1-yl)-

imidazole, 1-butanyl-imidazole, sec-butylcyclopropane, 2-(ethylsulfonyl)proparyl, 1-isobutylpyrrolidine, 4-pyridyl 1-oxide, and 5-benzo[c][1,2,5]oxadiazolyl 1-oxide, each of which is optionally substituted with one, two, or three substituents independently selected from the group consisting of halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, C₁₋₆ alkyl, haloalkyl, hydroxyalkyl, (carboxamido)alkyl, (cycloalkyl)alkyl, optionally substituted C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 5- to 14-membered heteroaryl, optionally substituted 4- to 14-membered heterocyclo, aralkyl, -N(H)C(=O)R⁶, -C(=O)R⁷, and -S(=O)₂R⁸;

Y is selected from the group consisting of -C(R^{5a})(R^{5b})C(=O)-, -C(=O)-, and -S(=O)₂-;

B is selected from the group consisting of C₁₋₁₀ alkylenyl, optionally substituted C₃₋₁₂ cycloalkylenyl, optionally substituted C₆₋₁₄ arylenyl, optionally substituted 4- to 14-membered heterocyclenyl, and -C(H)R¹R²,

with the proviso that B is not optionally substituted pyrrolidinenyl;

X is selected from the group consisting of -N(R³)-, -S(=O)₂-, -S(=O)₂N(R³)-, -N(R³)S(=O)₂-, -S(=O)₂C(R⁴)(H)-, -C(=O)-, -C(=O)N(R³)-, -N(R³)C(=O)-, -C(=O)O-, -OC(=O)-, -C(=O)C(R⁴)(H)N(R³)-, -N(R³)C(=O)C(R⁴)(H)-, and -C(=O)C(R⁴)(H)-; or X is absent;

Z is selected from the group consisting of hydrogen, optionally substituted C₁₋₆ alkyl, fluoroalkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, (cycloalkyl)alkyl, (amino)(hydroxy)alkyl, (amino)(aryl)alkyl, (hydroxy)(aryl)alkyl, (aralkylamino)alkyl, (hydroxyalkylamino)alkyl, alkoxyalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C₃₋₁₂ cycloalkyl, aralkyl, and (heteroaryl)alkyl; or

Z is $-\text{CH}(\text{R}^{9a})(\text{R}^{9b})$;

R^{9a} is selected from the group consisting of hydrogen, C_{1-6} alkyl, fluoroalkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, alkoxyalkyl, optionally substituted C_{6-14} aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C_{3-12} cycloalkyl, aralkyl, and (heteroaryl)alkyl;

R^{9b} is selected from the group consisting of optionally substituted C_{6-14} aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C_{3-12} cycloalkyl, aralkyl, and (heteroaryl)alkyl;

R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, optionally substituted C_{3-12} cycloalkyl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted C_{6-14} aryl, aralkyl, and alkoxycarbonyl.

R^2 is selected from the group consisting of C_{1-6} alkyl, optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted 5- to 14-membered heteroaryl, optionally substituted 4- to 14-membered heterocyclo, and (heteroaryl)alkyl;

R^3 is selected from the group consisting of hydrogen and C_{1-4} alkyl; and

R^4 is selected from the group consisting of hydrogen, C_{1-4} alkyl, hydroxy, amino, alkylamino, dialkylamino, cycloalkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, and hydroxyalkyl.

R^{5a} is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R^{5b} is selected from the group consisting of hydrogen, C_{1-4} alkyl, and 4- to 14-membered heterocyclo;

R^6 is C_{1-4} alkyl,

R^7 is C_{1-4} alkyl; and

R^8 is selected from the group consisting of C_{1-4} alkyl, amino, alkylamino, and dialkylamino,

wherein -X-Z is attached to any available carbon or nitrogen atom of B, R^1 , or R^2 ,

with the proviso that said compound having Formula I is not N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)benzamide.

2. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is C_{1-10} alkylene.

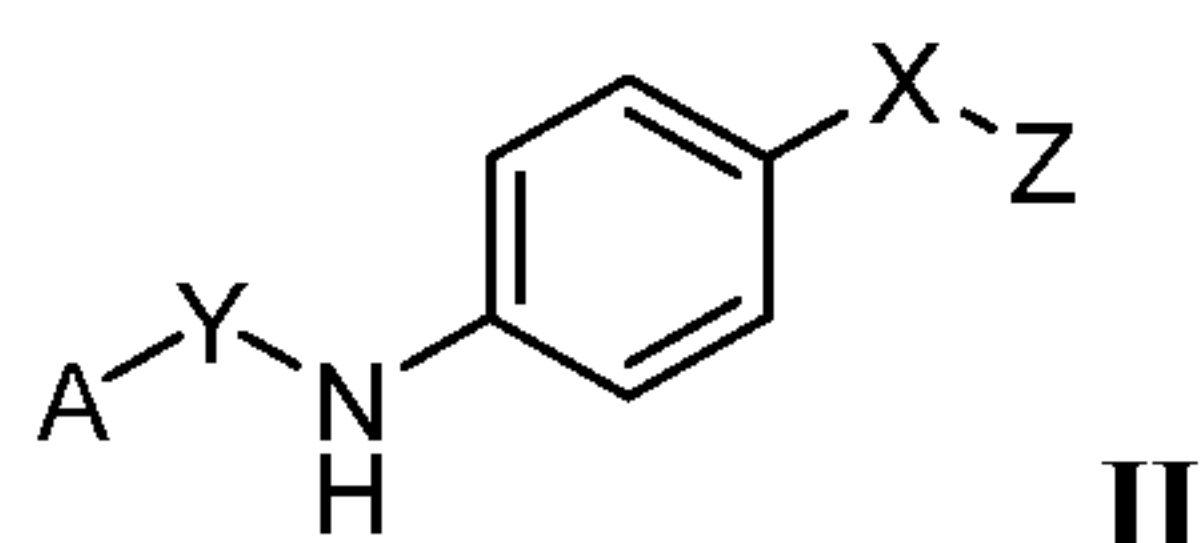
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt or hydrate thereof, wherein, X is selected from the group consisting of $-N(R^3)C(=O)C(R^4)(H)-$ and $-N(R^3)C(=O)-$.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or hydrate thereof, wherein Z is selected from the group consisting of C_{1-6} alkyl and (amino)alkyl.

5. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is optionally substituted C_{6-14} arylene.

6. The compound of claim 5, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is divalent form of optionally substituted phenyl.

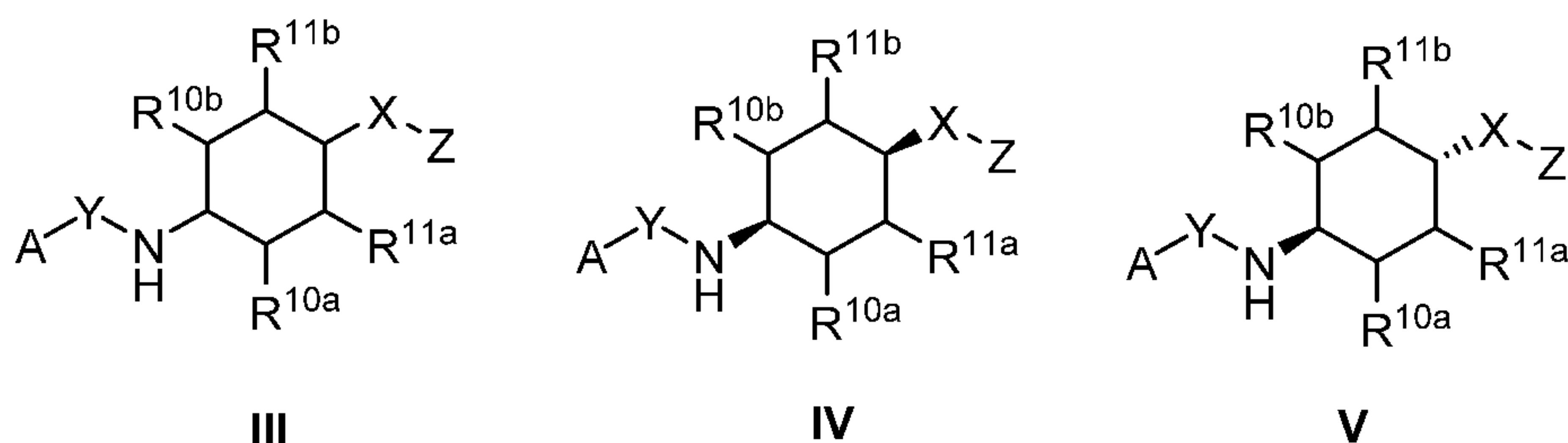
7. The compound of claim 6, or a pharmaceutically acceptable salt or hydrate thereof, having Formula II:



wherein X is absent and Z is (amino)alkyl.

8. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is optionally substituted C₃₋₁₂ cycloalkylenyl.

9. The compound of claim 8, or a pharmaceutically acceptable salt or hydrate thereof, having Formula **III**, Formula **IV**, or Formula **V**:



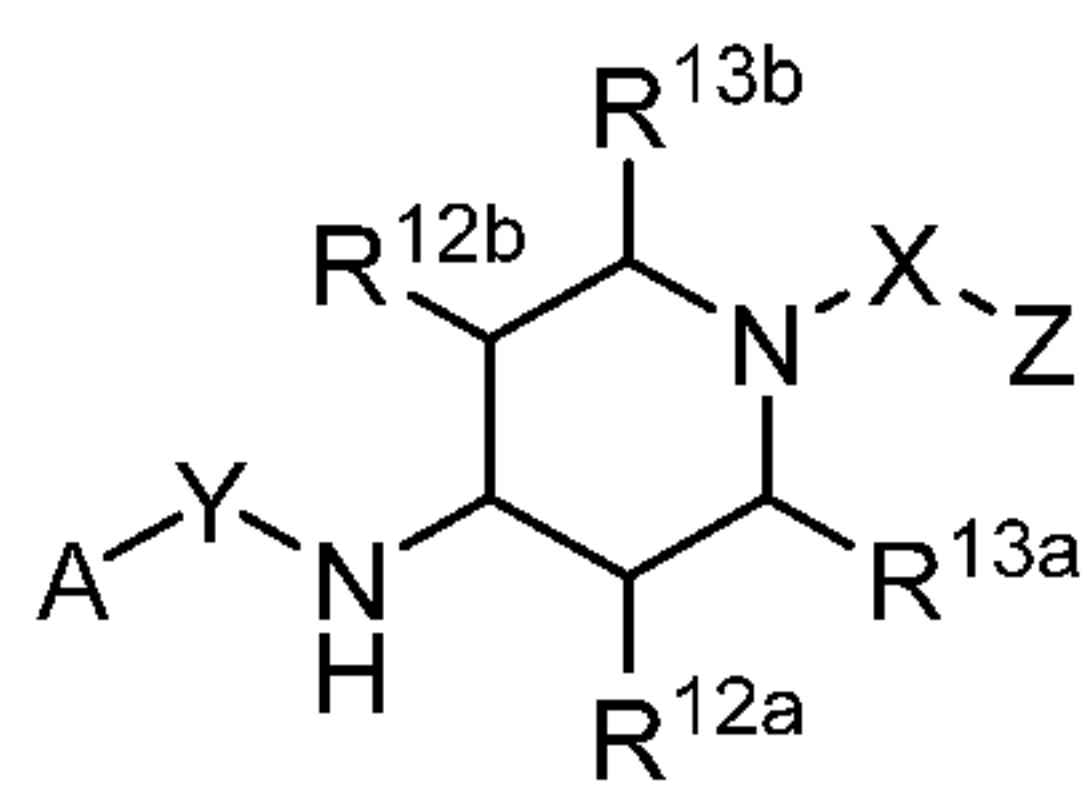
wherein R^{10a}, R^{10b}, R^{11a}, and R^{11b} are each independently selected from the group consisting of hydrogen and C₁₋₄ alkyl.

10. The compound of claim 9, or a pharmaceutically acceptable salt or hydrate thereof, wherein X is -N(R³)C(=O)- and Z is (amino)alkyl.

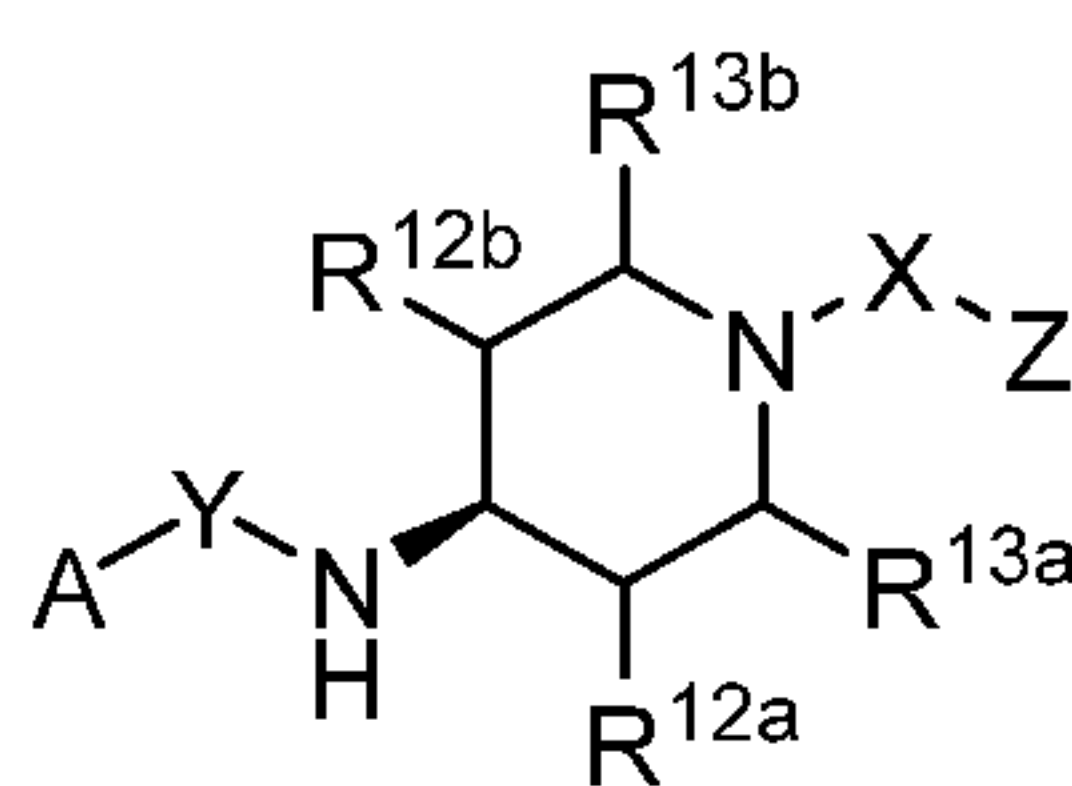
11. The compound of claim 9, or a pharmaceutically acceptable salt or hydrate thereof, wherein X is -N(R³)- and Z is hydrogen.

12. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is optionally substituted 4- to 14-membered heterocyclenyl.

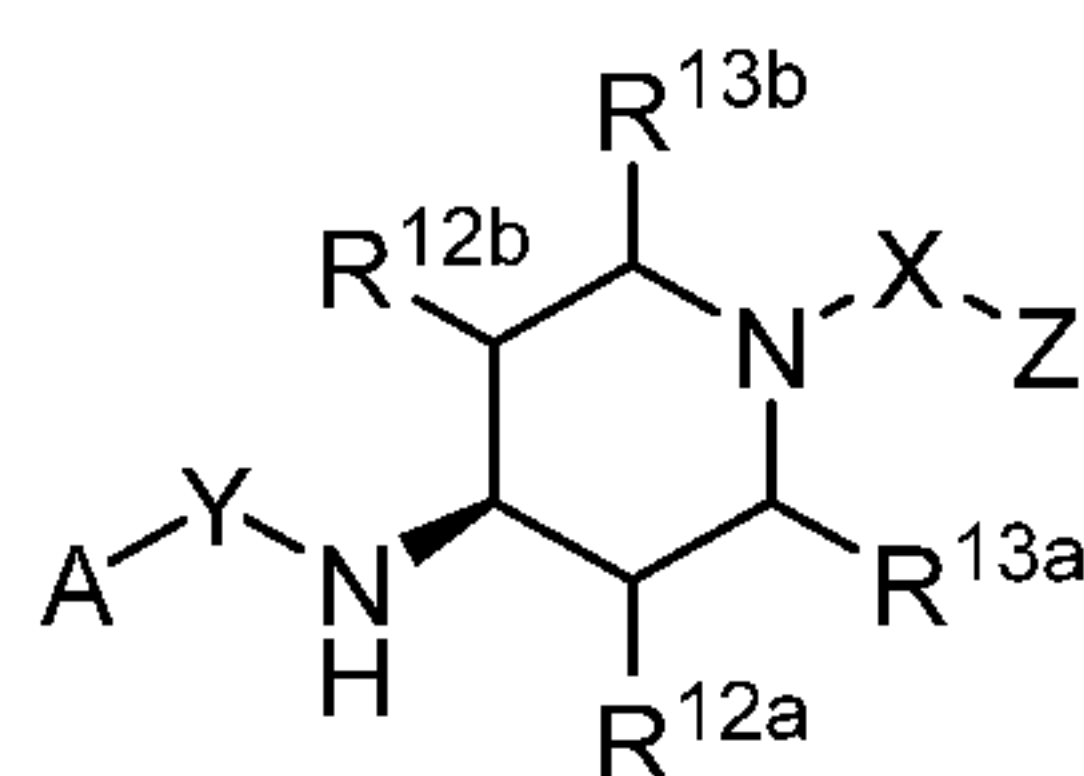
13. The compound of claim 12, or a pharmaceutically acceptable salt or hydrate thereof, having Formula **VI**, Formula **VII**, or Formula **VIII**:



VI



VII



VIII

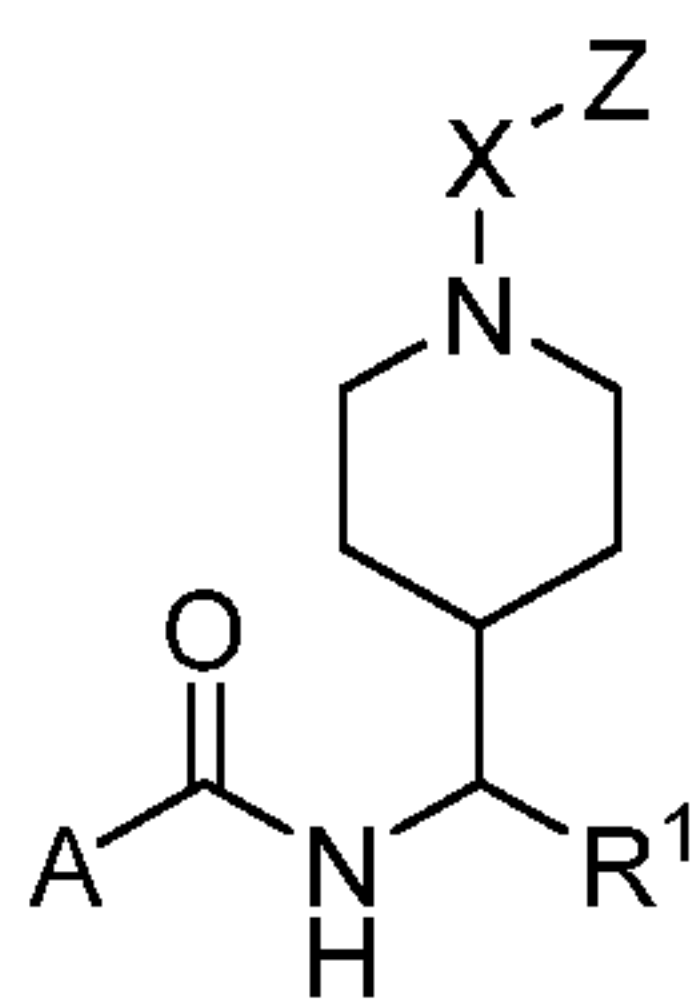
wherein R^{12a} , R^{12b} , R^{13a} , and R^{13b} are each independently selected from the group consisting of hydrogen and C_{1-4} alkyl.

14. The compound of claim 13, or a pharmaceutically acceptable salt or hydrate thereof, wherein X is selected from the group consisting of $-C(=O)C(R^4)(H)-$, $-C(=O)-$, and $-S(=O)_2-$; and R^4 is selected from the group consisting of hydrogen and amino.

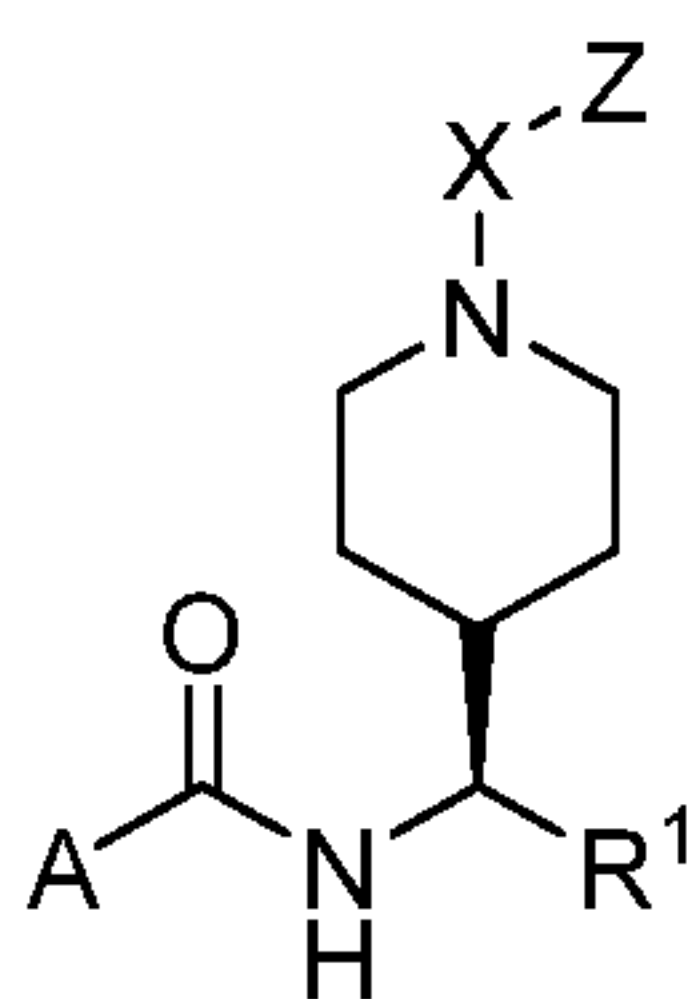
15. The compound of claim 14, or a pharmaceutically acceptable salt or hydrate thereof, wherein Z is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, aralkyl, and (hetaroaryl)alkyl.

16. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is $-C(H)R^1R^2$.

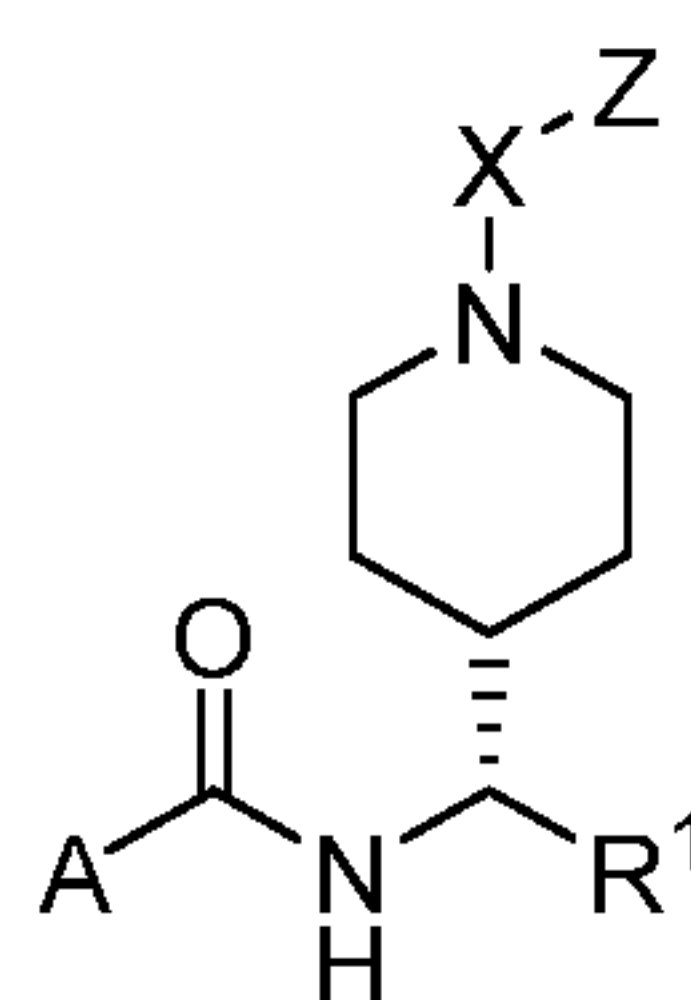
17. The compound of claim 16, or a pharmaceutically acceptable salt or hydrate thereof, having Formula IX, Formula X, or Formula XI:



IX



X



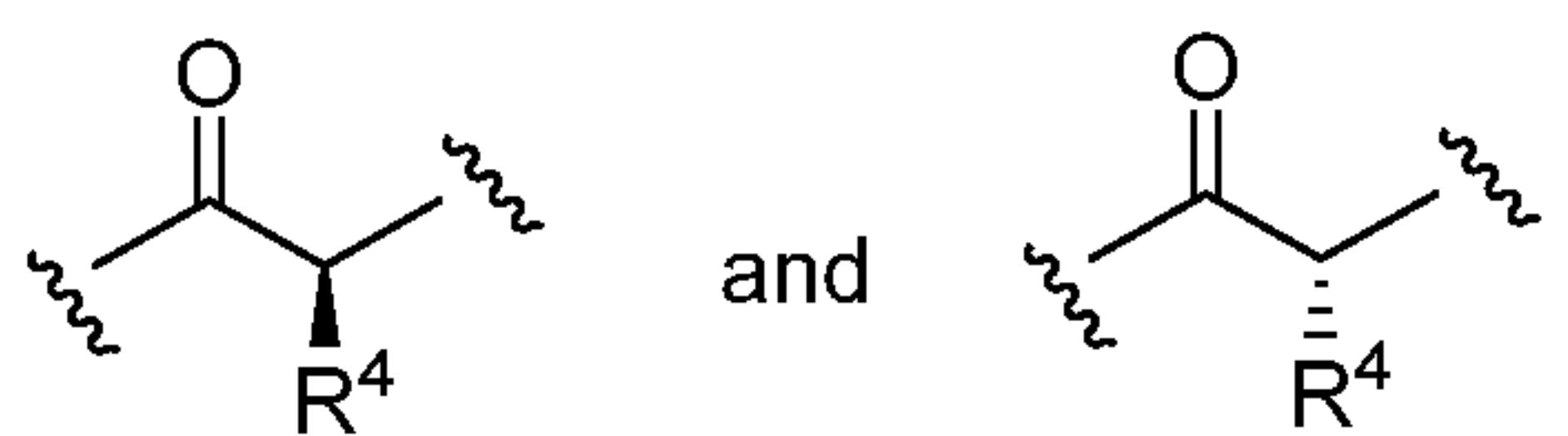
XI

18. The compound of claim 17, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, alkoxycarbonyl, and optionally substituted C_{6-14} aryl.

19. The compound of claim 18, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^1 is selected from the group consisting of hydrogen and methyl.

20. The compound of claim 19, or a pharmaceutically acceptable salt or hydrate thereof, wherein X is $-C(=O)C(R^4)(H)-$ and R^4 is amino.

21. The compound of claim 20, or a pharmaceutically acceptable salt or hydrate thereof, wherein X is selected from the group consisting of:



22. The compound of claim 21, or a pharmaceutically acceptable salt or hydrate thereof, wherein Z is C_{1-6} alkyl.

23. The compound of claim 22, or a pharmaceutically acceptable salt or hydrate thereof, wherein Z is methyl.

24. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt or hydrate thereof, wherein Y is $-C(R^{5a})(R^{5b})C(=O)-$.

25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{5a} and R^{5b} are each independently selected from the group consisting of hydrogen and methyl.

26. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt or hydrate thereof, wherein Y is $-S(=O)_2-$.

27. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt or hydrate thereof, wherein Y is $-C(=O)-$.

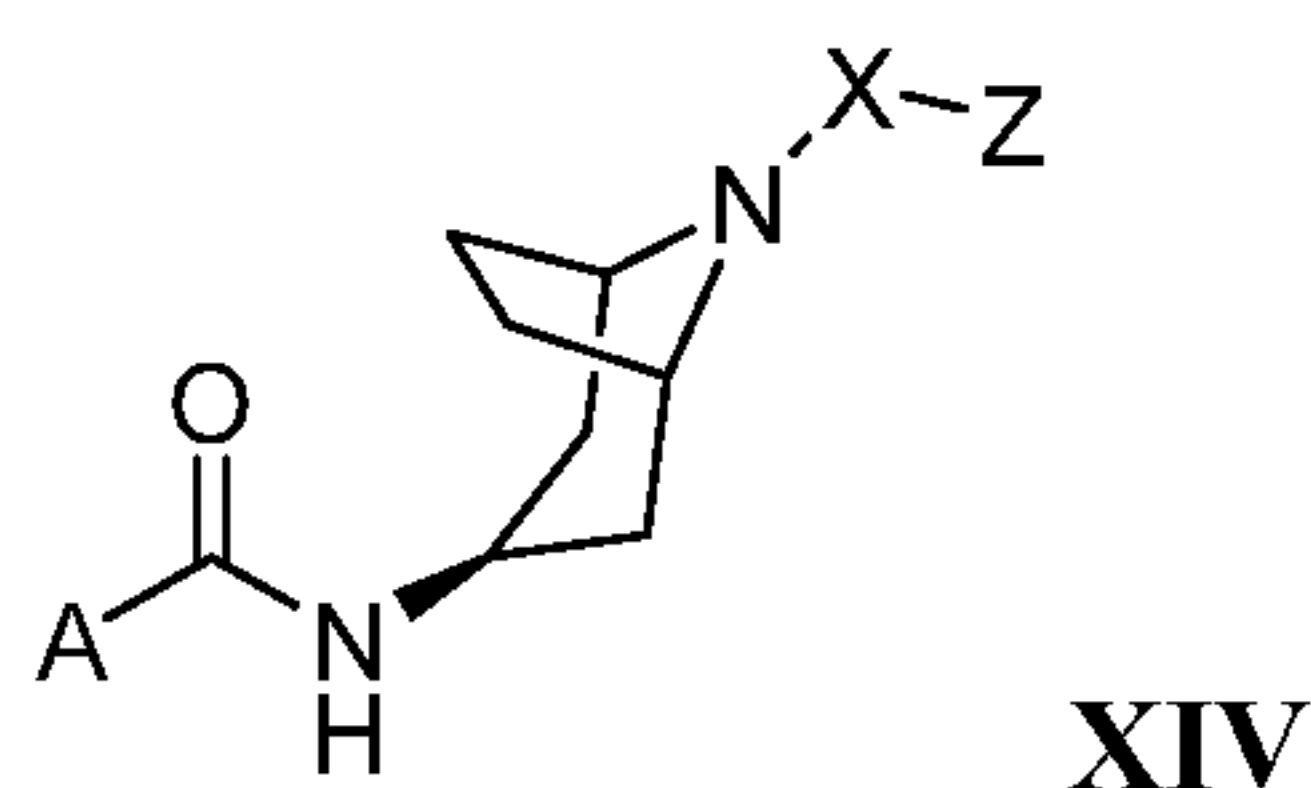
28. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt or hydrate thereof, wherein A is selected from the group consisting of 1,2,3-triazolyl, 1,2,4-triazolyl, 2-(1,2,3,4-tetrahydroquinoliny), 2-indolyl, 2-thiazolyl, 3-(1,2,4-

oxadiazolyl), 3-isothiazolyl, 5-(1,3-dihydro-2H-benzo[d]imidazolyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-b]pyridinyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-c]pyridinyl-2-one), 5-(2,2-difluorobenzo[d][1,3]dioxolyl), 5-benzo[d]oxazolyl-2(3H)-one, 5-indolinyl-2-one, 6-benzo[b][1,4]oxazinyl-3-one, and 6-isoquinolinyl.

29. The compound of claim 28, or a pharmaceutically acceptable salt or hydrate thereof, wherein A is 5-indolinyl-2-one.

30. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein Y is -C(=O)- and A is selected from the group consisting of 5-indolinyl-2-one and 1,2,3-triazolyl.

31. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, having Formula **XIV**:



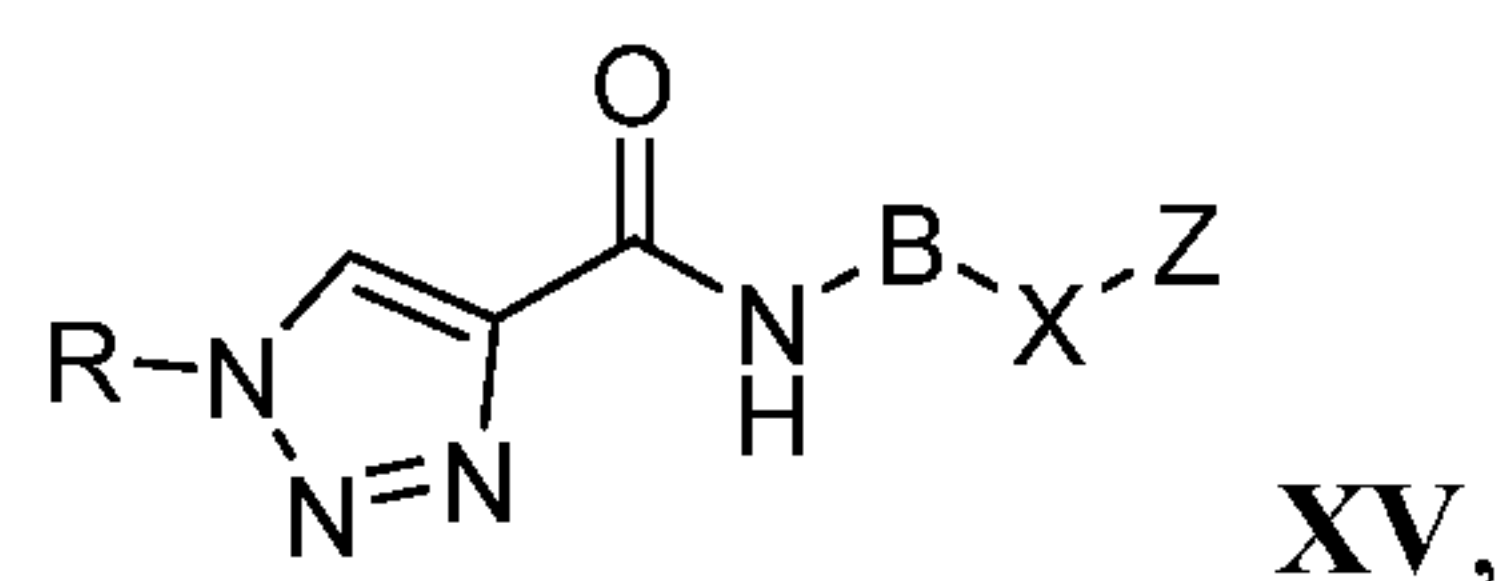
32. The compound of claim 31, or a pharmaceutically acceptable salt or hydrate thereof, wherein A is 5-indolinyl-2-one that is optionally substituted with one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, C₁₋₆ alkyl, haloalkyl, and hydroxyalkyl.

33. The compound of claim 32, or a pharmaceutically acceptable salt or hydrate thereof, wherein A is 6-chloro-5-indolinyl-2-one.

34. The compound of any one of claims 31-33, or a pharmaceutically acceptable salt or hydrate thereof, wherein X is selected from the group consisting of S(=O)₂- and -S(=O)₂C(R⁴)(H)-.

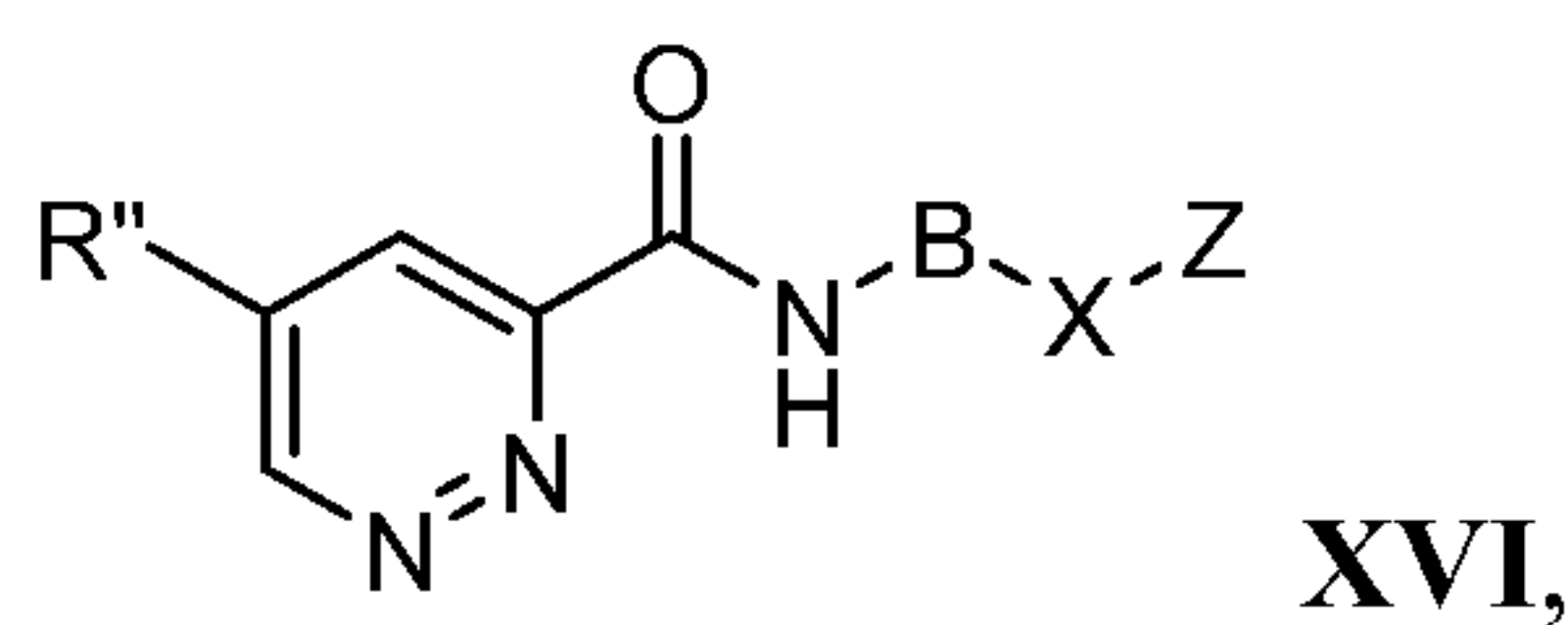
35. The compound of claim 34, or a pharmaceutically acceptable salt or hydrate thereof, Z is selected from the group consisting of optionally substituted C₆₋₁₄ aryl, optionally substituted 4- to 14-membered heterocyclo, and optionally substituted C₃₋₁₂ cycloalkyl.

36. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, having Formula **XV**:



wherein R is selected from the group consisting of C₁₋₆ alkyl and C₃₋₁₂ cycloalkyl; and B is optionally substituted 4- or 6- to 14-membered heterocyclenyl.

37. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, having Formula **XV**:



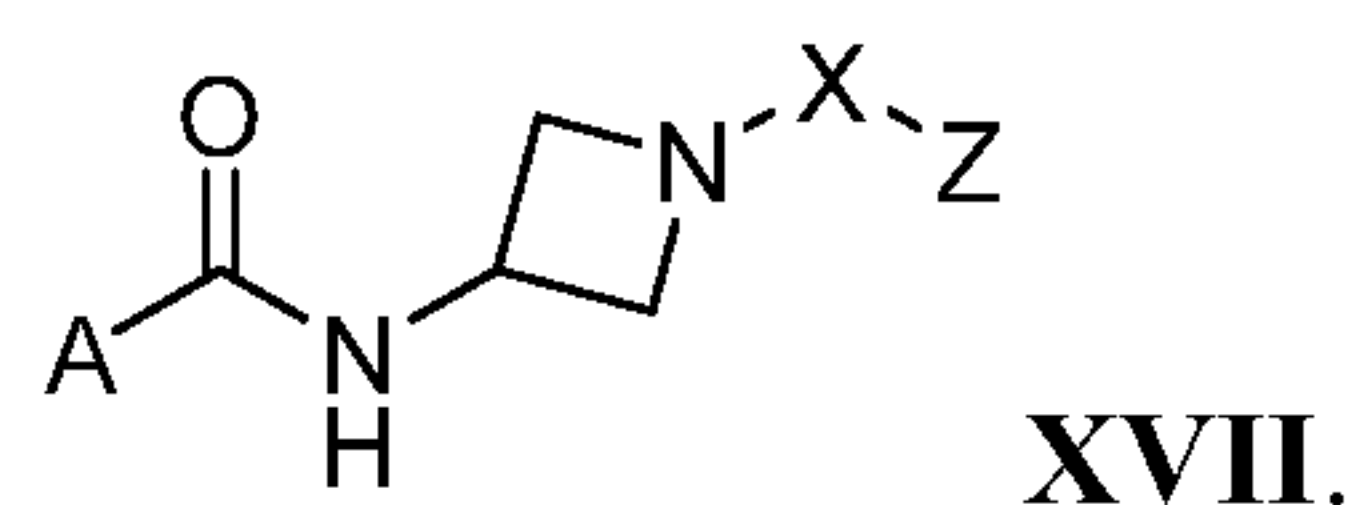
wherein R'' is selected from the group consisting of C₁₋₆ alkyl and C₃₋₁₂ cycloalkyl; and B is optionally substituted 4- or 6- to 14-membered heterocyclenyl.

38. The compound of claim 36 or 37, or a pharmaceutically acceptable salt or hydrate thereof, wherein X is absent.

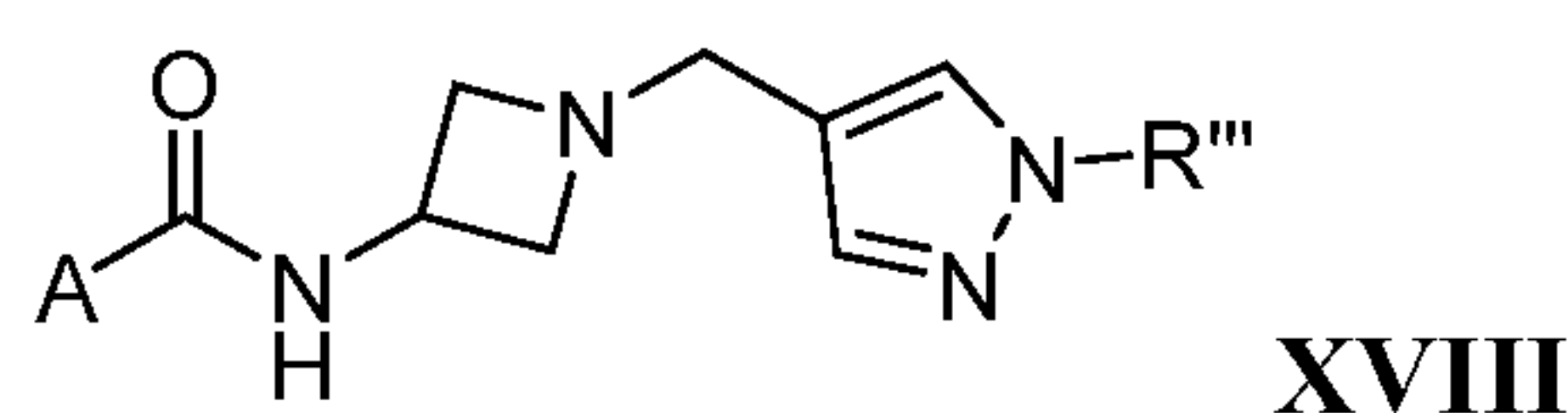
39. The compound of claim 36-38, or a pharmaceutically acceptable salt or hydrate thereof, wherein Z is selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₃₋₁₂ cycloalkyl, aralkyl, and (heteroaryl)alkyl, or Z is -CH(R^{9a})(R^{9b}).

40. The compound of claim 36-39, or a pharmaceutically acceptable salt or hydrate thereof, wherein Z is selected from the group consisting of aralkyl and (heteroaryl)alkyl.

41. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, having Formula **XVII**



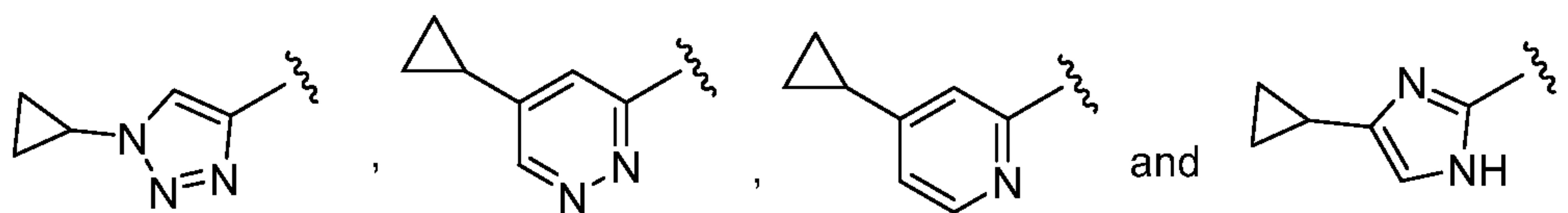
42. The compound of claim 41, or a pharmaceutically acceptable salt or hydrate thereof, having Formula **XVIII**:



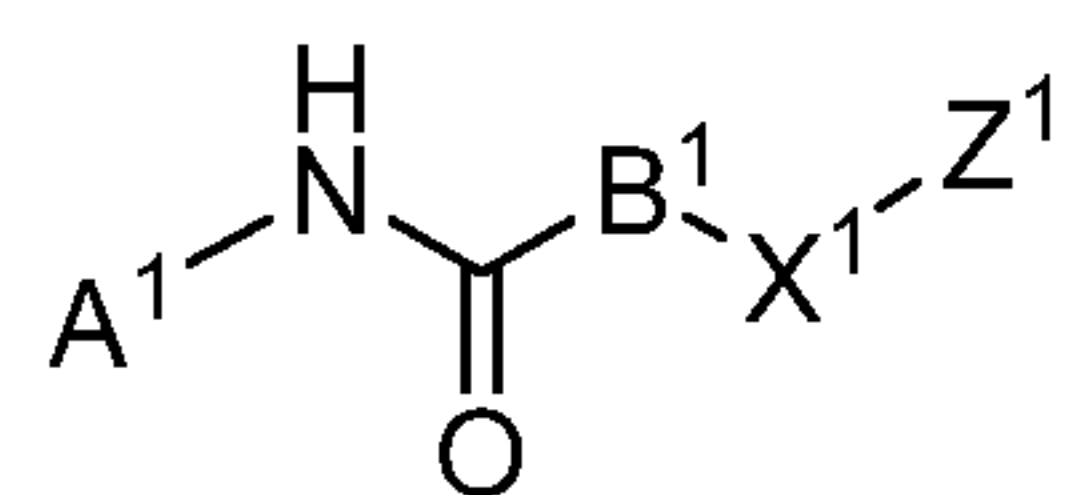
wherein R''' is selected from the group consisting of aralkyl and (heteroaryl)alkyl.

43. The compound of claim 42, or a pharmaceutically acceptable salt or hydrate thereof, wherein A is selected from the group consisting of 1,2,3-triazolyl, 3-pyridazinyl, 2-pyridyl, and 2-imidazolyl, each of which is substituted with one substituent selected from the group consisting of C₁₋₆ alkyl and C₃₋₆ cycloalkyl.

44. The compound of claim 43, or a pharmaceutically acceptable salt or hydrate thereof, wherein A is selected from the group consisting of



45. A compound having Formula **XII**:



or a pharmaceutically acceptable salt or hydrate thereof,
wherein:

A¹ is selected from the group consisting of 1,2,3-triazolyl, 1,2,4-triazolyl, 1-imidazolyl, 1-isoquinoliny, 1-pyrazolyl, 2-(1,2,3,4-tetrahydroquinoliny),

2-benzo[d]imidazolyl, 2-benzo[d]thiazolyl, 2-chromenyl-4-one, 2-furanyl, 2-imidazo[1,2-b]pyridazinyl, 2-imidazolyl, 2-indolyl, 2-naphthalenyl, 2-pyrazinyl, 2-pyridyl, 2-pyrimidinyl, 2-pyrrolidinyl, 2-pyrrolyl, 2-quinoliny, 2-quinoxaliny, 2-thiazolo[5,4-c]pyridinyl, 2-thiazolyl, 2-thiophenyl, 3-(1,2,3,4-tetrahydroisoquinoline), 3-(1,2,4-oxadiazolyl), 3-imidazo[1,2-a]pyrimidinyl, 3-indazolyl, 3-indolyl, 3-isothiazolyl, 3-pyrazolyl, 3-pyridazinyl, 3-pyridinyl-2-one, 3-pyridyl, 3-pyrrolo[3,2-b]pyridinyl, 3-quinoliny, 4-(2,2-difluorobenzo[d][1,3]dioxolyl), 4-cyclohexanyl-1-amine, 4-imidazolyl, 4-indoliny-2-one, 4-indolyl, 4-isothiazolyl, 4-oxazolyl, 4-piperidinyl, 4-pyrazolyl, 4-pyridyl, 4-quinoliny, 5-(1,3-dihydro-2H-benzo[d]imidazolyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-b]pyridinyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-c]pyridinyl-2-one), 5-(2,2-difluorobenzo[d][1,3]dioxolyl), 5-(2,4-dihydro-3H-1,2,4-triazolyl-3-one), 5-4H-furo[3,2-b]pyrrolyl, 5-benzo[c][1,2,5]oxadiazolyl, 5-benzo[d][1,3]dioxolyl, 5-benzo[d]oxazolyl-2(3H)-one, 5-bicyclo[2.2.1]heptyl-2-ene, 5-indoliny-2,3-dione, 5-indoliny-2-one, 5-indolyl, 5-isoindoliny-1-one, 5-isoxazolyl, 5-pyrazolo[3,4-c]pyridinyl, 5-pyrazolyl, 5-pyrimidinyl, 5-thiazolyl, 6-(1,2,3,4-tetrahydronaphthalenyl), 6-(3,4-dihydroquinoliny-2(1H)-one), 6-(3,4-dihydroquinoxaliny-2(1H)-one), 6-(4,5-dihydropyridazinyl-3(2H)-one), 6-benzo[b][1,4]oxazinyl-3-one, 6-benzo[d]imidazolyl, 6-benzo[d]oxazolyl-2(3H)-one, 6-benzo[d]thiazolyl, 6-chromenyl-2-one, 6-imidazo[2,1-b]thiazole, 6-indazolyl, 6-indoliny-2-one, 6-indolyl, 6-isoquinoliny, 6-quinoliny, 6-quinoxaliny, 6-quinoxaliny-2(1H)-one, 7-(3,4-dihydroquinoliny-2(1H)-one), 7-(3,4-dihydroquinoxalin-2(1H)-one), 7-benzo[b][1,4]oxazinyl-3-one, 7-indoliny-2-one, 7-quinoliny, 8-benzo[b][1,4]oxazinyl-3-one, cyclopropanyl, phenyl, 4-(prop-1-en-1-yl)-imidazole, 1-butanyl-imidazole, sec-butylcyclopropane, 2-(ethylsulfonyl)propanyl, 1-isobutylpyrrolidine, 4-pyridyl 1-oxide, and 5-benzo[c][1,2,5]oxadiazolyl 1-oxide, each of which is optionally substituted with one, two, or three substituents independently selected from the group consisting of halo, hydroxy,alkoxy, amino, alkylamino, dialkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, C₁₋₆ alkyl, haloalkyl, hydroxyalkyl, (carboxamido)alkyl, (cycloalkyl)alkyl, optionally substituted C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 5- to 14-membered heteroaryl, optionally substituted 4- to 14-membered heterocyclo, and aralkyl;

B¹ is selected from the group consisting of optionally substituted C₃₋₁₂ cycloalkylenyl and optionally substituted 4- to 14-membered heterocyclenyl,

X¹ is selected from the group consisting of -N(R^{3a})-, -S(=O)₂-, -S(=O)₂N(R^{3a})-, -N(R^{3a})S(=O)₂-, -S(=O)₂C(R^{4a})(H)-, -C(=O)-, -C(=O)N(R^{3a})-, -N(R^{3a})C(=O)-, -C(=O)O-, -OC(=O)-, -C(=O)C(R^{4a})(H)N(R^{3a})-, -N(R^{3a})C(=O)C(R^{4a})(H)-, and -C(=O)C(R^{4a})(H)-; or X¹ is absent;

Z¹ is selected from the group consisting of hydrogen, optionally substituted C₁₋₆-alkyl, fluoroalkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, (cycloalkyl)alkyl, (amino)(hydroxy)alkyl, (amino)(aryl)alkyl, (hydroxy)(aryl)alkyl, (aralkylamino)alkyl, (hydroxyalkylamino)alkyl, alkoxyalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C₃₋₁₂ cycloalkyl, aralkyl, and (heteroaryl)alkyl;

R^{3a} is selected from the group consisting of hydrogen and C₁₋₄ alkyl; and

R^{4a} is selected from the group consisting of hydrogen, C₁₋₄ alkyl, hydroxy, amino, alkylamino, and dialkylamino.

46. The compound of claim 45, or a pharmaceutically acceptable salt or hydrate thereof, wherein A¹ is 5-indolinyl-2-one.

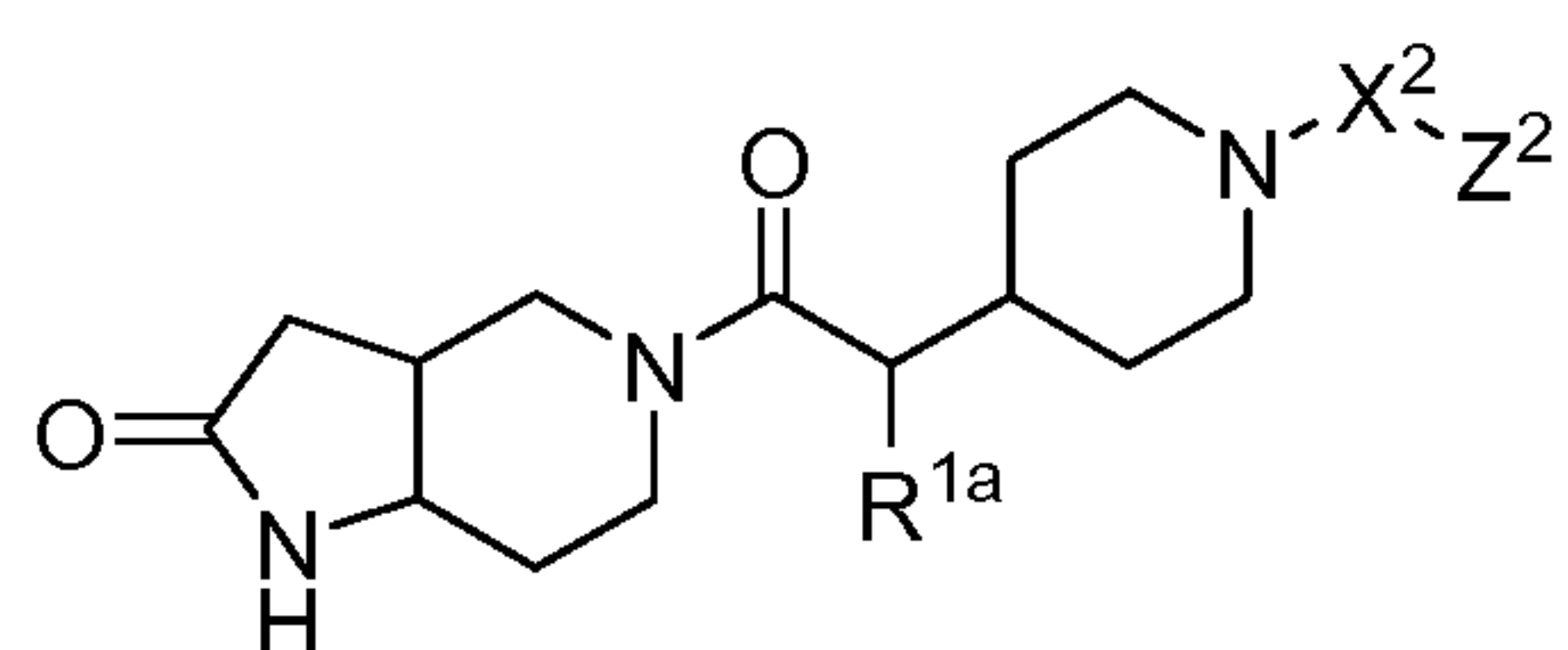
47. The compound of claims 45 or 46, or a pharmaceutically acceptable salt or hydrate thereof, wherein B¹ is optionally substituted C₃₋₁₂ cycloalkylenyl.

48. The compound of any one of claims 45-47, or a pharmaceutically acceptable salt or hydrate thereof, wherein X¹ is selected from the group consisting of -S(=O)₂- and -C(=O)-.

49. The compound of any one of claims 45-48, or a pharmaceutically acceptable salt or hydrate thereof, wherein Z^1 is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, and (dialkylamino)alkyl.

50. The compound of claim 45, or a pharmaceutically acceptable salt or hydrate thereof, which is (1r,4r)-4-(3-aminopropanamido)-N-(2-oxoindolin-5-yl)cyclohexane-1-carboxamide.

51. A compound having Formula **XIII**:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X^2 is selected from the group consisting of $-N(R^{3b})-$, $-S(=O)_2-$, $-S(=O)_2N(R^{3b})-$, $-N(R^{3b})S(=O)_2-$, $-S(=O)_2C(R^{4b})(H)-$, $-C(=O)-$, $-C(=O)N(R^{3b})-$, $-N(R^{3b})C(=O)-$, $-C(=O)O-$, $-OC(=O)-$, $-C(=O)C(R^{4b})(H)N(R^{3b})-$, $-N(R^{3b})C(=O)C(R^{4b})(H)-$, and $-C(=O)C(R^{4b})(H)-$; or X is absent;

Z^2 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, fluoroalkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, (cycloalkyl)alkyl, (amino)(hydroxy)alkyl, (amino)(aryl)alkyl, (hydroxy)(aryl)alkyl, (aralkylamino)alkyl, (hydroxyalkylamino)alkyl, alkoxyalkyl, optionally substituted C_{6-14} aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl optionally substituted C_{3-12} cycloalkyl, aralkyl, and (heteroaryl)alkyl;

R^{1a} is selected from the group consisting of hydrogen, C_{1-6} alkyl, and optionally substituted C_{6-14} aryl;

R^{3b} is selected from the group consisting of hydrogen and C_{1-4} alkyl; and

R^{4b} is selected from the group consisting of hydrogen, C_{1-4} alkyl, hydroxy, amino, alkylamino, and dialkylamino.

52. The compound of claim 51, or a pharmaceutically acceptable salt or hydrate thereof, wherein X^2 is selected from the group consisting of $-S(=O)_2-$ and $-C(=O)-$.

53. The compound of claims 51 or 52, or a pharmaceutically acceptable salt or hydrate thereof, wherein Z^2 is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, and (dialkylamino)alkyl.

54. The compound of claim 51, or a pharmaceutically acceptable salt or hydrate thereof, wherein X^2 is absent; and Z^2 is hydrogen.

55. The compound of any one of claims 51-54, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{1a} is selected from the group consisting of hydrogen and methyl.

56. The compound of claim 51, or a pharmaceutically acceptable salt or hydrate thereof, selected from the group consisting of 5-(2-(piperidin-4-yl)acetyl)octahydro-2H-pyrrolo[3,2-c]pyridin-2-one and 5-(2-(1-(3-aminopropanoyl)piperidin-4-yl)acetyl)octahydro-2H-pyrrolo[3,2-c]pyridin-2-one.

57. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, selected from any one or more of the compounds provided in Table 1, Table 1A, Table 3, Table 3A, Table 4, Table 4A, Table 5, Table 6 or Table 6A of the specification.

58. The compound of claim 57, or a pharmaceutically acceptable salt or hydrate thereof, selected from the group consisting of:

rel-N-{1-[(1S)-1-[2-chloro-3-(2-hydroxyethoxy)phenyl]ethyl]azetidin-3-yl}-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide;

N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide;

N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-4-cyclopropylpicolinamide;

N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide;

N-(1-((1-(4-chlorobenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-4-cyclopropyl-1H-imidazole-2-carboxamide; and

1-cyclopropyl-N-(1-((1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methyl)azetidin-3-yl)-1H-1,2,3-triazole-4-carboxamide.

59. A pharmaceutical composition comprising the compound of any one of claims 1-58, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

60. A method of treating a patient comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-58, or a pharmaceutically acceptable salt or hydrate thereof, wherein the patient has cancer.

61. The method of claim 60, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma,

cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma peritonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma,

skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

62. The pharmaceutical composition of claim 59 for use in treating cancer.

63. The pharmaceutical composition of claim 62, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor,

gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocyoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine

cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

64. A compound of any one of claims 1-58, or a pharmaceutically acceptable salt or hydrate thereof, for use in treatment of cancer.

65. The compound of claim 64, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma,

non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

66. Use of a compound of any one of claims 1-58, or a pharmaceutically acceptable salt or hydrate thereof, for the manufacture of a medicament for treatment of cancer.

67. The use of claim 66, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer,

MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

68. A kit comprising the compound of any one of claims 1-58, or a pharmaceutically acceptable salt or hydrate thereof, and instructions for administering the compound, or a pharmaceutically acceptable salt or hydrate thereof, to a patient having cancer.

69. The kit of claim 68, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic

leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer,

mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

70. A method of treating a SMYD protein mediated disorder comprising administering to a subject in need thereof a compound of any one of claims 1-58, or a pharmaceutically acceptable salt or hydrate thereof in an effective amount to treat the SMYD protein mediated disorder.

